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Health Technology Clinical Committee Public Meeting

November 22, 2019

Gregory Brown: OK. Ladies and gentlemen, I think we are ready to get started today. I'm Greg Brown. I am the Chair of the Health Technology Clinical Committee. Today, we are meeting to discuss whole exome sequencing, as well as hip surgery procedures for treatment of femoral acetabular impingement syndrome, which is a rereview. So, we will start with our update from our program director.

Josh Morse: OK. Thank you, Dr. Brown. I am Josh Morse. I am a Health Technology Assessment program director from the Health Care Authority and as was stated, today's topics are whole exome sequencing, which is a new topic, and the update to surgery for FAI, or femoral acetabular impingement syndrome. So, a couple meeting reminders. We do record this meeting, and the technology is pretty sensitive. So, when you are speaking, please try to remember to state your name before you talk for our transcriptionist. The transcript of the proceedings will be made available on the Health Technology Assessment program website. The URL is here on this slide. I went through the third bullet there. To provide public comment today, if you have signed up in advance, there is a signup table outside the room here for . . . there are different forms for this morning's topic, and a separate form for the afternoon topic.

A little background about this program, the Health Technology Assessment program is administered through the Health Care Authority. It was created in 2006 through a legislation that was designed to use evidence reports and a panel of clinicians to make coverage decisions for selected medical procedures and tests based on their evidence of safety, efficacy, and cost-effectiveness.

Multiple state agencies participate to identify topics, and ultimately to implement the policy decisions that come from this process. They included the Health Care Authority, which operates the Uniform Medical Plan and the state Medicaid program, or Apple Health. The Department of Labor

and Industries, and the Department of Corrections. Agencies implement the determinations from the program, within their existing statutory frameworks.

The purpose of this program and this process is ensure that medical treatments, devices, and services that are paid for with State healthcare dollars are safe and proven to work. We, in the program, provide resources for State agencies that are purchasing healthcare. We work to develop scientific evidence based reports on medical devices, procedures, and tests that are selected for review, and we facilitate and provide staff support to this independent clinical committee of healthcare practitioners, and this group determines which of those medical devices, procedures, or tests meet the requirements for coverage in terms of safety, efficacy, and cost-effectiveness.

This is a very high-level view of the process, by which technologies are selected and ultimately how we get here for a decision and then implementation. Anyone may nominate topics for review. The Health Care Authority director has the authority to select topics that go through this process. Once selected, they go through a key question development process to outline the research that will be done. A Technology Assessment Center, or TAC, sometimes we refer to them as EPC's, or Evidence Practice Centers, they then are charged with producing a report. There are multiple comment periods throughout this process, including on the draft report. Finally, that report comes here to the public meeting, where it is considered by this group, the Health Technology Clinical Committee.

This is the calendar of activities beyond today's meeting for the Health Technology Clinical Committee. The next meeting is January 17th, next year. The topic for that meeting is cell-free DNA prenatal screening for chromosomal aneuploidies. In March, there is one topic scheduled. It is stem cell therapy for musculoskeletal conditions. Right now, for the May 15, 2020 meeting, there are two topics, tinnitus, which is actually a new topic, not a rereview, and a rereview of vagal nerve stimulation for epilepsy and depression. That will be an update. We follow the May meeting with a brief webinar to conclude the work from the May meeting. Then, looking further out, the committee traditionally meets in September. Then, the working meeting begins again in November.

So, to participate in this program, you can visit the Health Care Authority website for the Health Technology Assessment program. You can sign up to receive emails from the program through our system. The information about that is on the Health Care Authority webpage. You can provide

comment on any of the proposed topics, key questions, or draft and final reports or draft decisions. That information is available on our website. If you're signed up for the emails, you will get notified when those opportunities are open. Anyone may attend these public meetings and present comments directly to the committee. Anyone, as stated before, may nominate technologies for review through this process. That concludes my updates. Thank you.

Mika Sinanan: Can I ask a question. In the process of the RFA, do we ask the TAC's whether they have done a review of the same topic in the recent past?

Josh Morse: You have that conversation. Yes. They're not independent . . . if you said RFA, referring to a contracting process?

Mika Sinanan: Yeah.

Josh Morse: So, we don't put individual contracts out for each topic. We have more global contracts. Then, we assign them annually.

Mika Sinanan: But you would ask, like, both . . . the group . . . has anybody done a review on this. Then, they're not starting from square one.

Josh Morse: Yes. We do try to find those opportunities.

Mika Sinanan: And do we know whether . . . if they've done it, whether they've used the same core analysis with an update? Part of the reason I ask this is, in other situations, we have seen consulting companies who have done reviews. Actually, when they make their presentations, they, sometimes, include old [inaudible] that are tailored to another organization, not the one that [inaudible]. It would be helpful to know whether they've done something before in the same area.

Josh Morse: Yes. We have . . . it's explicit when that does occur, when we know that we're basing something on prior work. Yeah. Thanks for the question.

Gregory Brown: Next order of business is we have . . . our last meeting was our retreat. So, we made no decision. So, there's no decision to review. We do have July minutes still to review if anybody had any comments or corrections, or anything needs to be changed?

Janna Friedly: Move to approve.

Gregory Brown: Second?

Seth Schwartz: Second.

Gregory Brown: OK. All in favor, aye?

Group: Aye.

Gregory Brown: Any opposed? Unanimously approved the minutes.

Josh Morse: Alright. Thank you.

Gregory Brown: OK. We will get onto our first topic, whole exome sequencing. The medical directors will be presenting first.

Charissa Fotinos: I feel very small behind this.

Gregory Brown: I'm sorry, Charissa. Can we . . . I need just a second. We usually actually introduce ourselves. We should do our . . . Dr. Yuen, let me introduce . . . let you introduce yourself first. Then, as a committee, we'll do it quickly and then, sorry.

Amy Yuen: My name is Amy Yuen. I am a medical geneticist at Mary Bridge Children's Hospital.

Gregory Brown: I'm Gregory Brown. I'm an orthopedic surgeon. I am with Franciscan Health in Tacoma and Federal Way.

Sheila Rege: Sheila Rege. Radiation oncologist from the Tri-Cities, Eastern Washington.

Seth Schwartz: Seth Schwartz. I'm a neuro-otologist at Virginia Mason here in Seattle.

Chris Hearne: I'm Chris Hearne. I'm a nurse practitioner. I work with Swedish Residential Care.

Tony Yen: I'm Tony Yen. I'm a hospitalist at Evergreen.

Janna Friedly: I'm Janna Friedly. I'm a physiatrist at the University of Washington.

John Bramhall: I'm John Bramhall. I'm an anesthesiologist and one of the medical directors at Harborview/University of Washington Medicine.

Laurie Mischley: My name is Laurie Mischley. I'm a naturopathic physician that works with people with Parkinson's Disease, research and practice.

Kevin Walsh: Kevin Walsh. I'm family medicine at Community Health of Central Washington in Ellensburg.

Mika Sinanan: Mika Sinanan. General surgeon working at the University.

Gregory Brown: Sorry, doctor. All good.

Charissa Fotinos: Good morning. My name is Charissa Fotinos. And I am the deputy chief medical officer for the Health Care Authority. I want to start by recognizing Dr. Brown who is currently the Chair of the committee, joined the committee in September of 2015, started to lead the committee in October of 2017. I just want to thank you. You've done a thoughtful, kind, and deliberate job in directing the committee through some really challenging topics that were not at all clear. So, on behalf of our agency, I really want to thank you for your time and effort, both of which have been quite substantial, and you will be missed. Thank you, very much.

Gregory Brown: You're welcome. It's been a pleasure.

Charissa Fotinos: We're going to talk about whole exome sequencing. This is a topic that . . . I'm sorry. This screen does not show that. So, I'm looking at the airport and trying to talk about this. So, in June 2017, we thought that we might include this with the chromosomal microarray, but as we went through the development of the key questions, it became clear that that was just too broad of a scope. So, as we got through that in September 2017, we narrowed the initial topic just to microarray. As there has been further progress, in terms of the technology and the ability to identify variance, in June 2019, we decided that we would proceed with whole exome sequencing as a stand standalone topic.

In terms of the agency medical directors' concerns, the concern was high for safety and medium both for efficacy and cost.

Clinical uses that you will see for WES just for short, so I don't stumble over it, but establishing a clinical diagnosis in a greater proportion of patients, that's the promise. Explaining phenotypic abnormalities that don't fall neatly into a previously described syndrome, enabling more appropriate and tailored patient management, the initiation of treatment can begin, or inappropriate treatment can be stopped, enabling patients to benefit from existing and emerging treatment trials, allowing accurate genetic counseling for family members, enabling carrier testing of at-risk relatives, offering the option of accurate prenatal or preimplantation diagnoses, and enabling predictive testing for late onset disorders. This is sort of not the complete universe but a broad swath of WES can be used for.

One of the things in our consideration of whether or not we should recommend coverage of this sort of relates to the fact of what is Medicaid's rule in terms of coverage. I like this slide because it sort of talks about there are different levels of consideration, pretty much for every intervention we have in clinical medicine. Really, Medicaid's rule is to buy health coverage for folks. So, really focusing on the individual level, we can have an understanding of what a person might be presenting with. We can get a perception of their disease risk. We can help people adjust to whatever diagnosis they may have. Or if one is not found, perhaps behavioral changes can occur at the individual level. As well, we can help people determine their future risk, perhaps. It might pave the way for further screening for other genetic diagnoses, individualized interventions, as well as longitudinal followup, as more conditions are identified over time, we can look back and say, well here's what we were not able to explain before. Pharmacogenomics can potentially help direct individual therapy and may ultimately be what we strive for in clinical medicine and improve the quality of life, reduce morbidity and mortality. From a health systems perspective, really it is not Medicaid's role to think about that, though it is, as a clinician, an exciting though. The more we learn, the more we know. So, that leads to a lot of system level ability to have broader understanding of things, ultimately building clinical workflows, decision tools to help providers make decisions related to genetics findings, and then look at healthcare utilization and cost-effectiveness at the higher level. I would prophet that that's really not Medicaid's role or consideration in thinking about this test. What kind of falls in the middle is really how does the findings, or do the results relate to the family members of the person who is being tested. People don't necessarily stay on Medicaid for their entire life, not the whole family is necessarily covered by Medicaid. So, how should that consideration be brought forward in terms of thinking about testing beyond just the proband, or person of interest.

The keys questions are as follows: In what proportion of patients does testing with WES result in either a clinically actionable finding, whether it's for treatment prevention of mitigation. An actual change to the patient's medical management or therapies, in terms of followup testing, medical monitoring, genetic counseling. What is the effect of the testing pathway that include WES on either medical management, genetic risk counseling compared to either testing sequences where WES was later in the sequencing of testing or early, as well.

Key question number two, what are the health outcomes, including mortality among patients who have WES testing and of the patients who

receive testing pathways that include WES, are there ideal ways in which those pathways should be undertaken to lead to sooner diagnoses and more effective care. Safety and harms: How many patients received erroneous results, whether that be false positive or false negative, what harms might be caused by these results, and how many patients experience these harms? What are the harms caused in terms of uncertain results that may be returned, or lack of diagnostic finding in the hopes of finding something to ascribe a set of symptoms to, or syndrome to. Then, how many patients received reports on ACMG-defined medically actionable variants after WES testing? What harms do those folks experience? How many patients experienced those harms? One could argue those are either harms or benefits, depending on your perspective. In this way, it's framed for harm. Then . . . yes?

Male: In your concerns, you said safety was a high [inaudible].

Charissa Fotinos: So, it doesn't really show up in the key questions, but are people going to get results that we don't know what they mean? Are there going to be results that may portend the development of Huntington's Chorea for instance, and that's not what you're looking for. So, results that may suggest something, what's the obligation to tell them, the ethics around it, so concerns around that, obviously concerns about how accurate. And then the meaning of a lot of variants of insignificant syndrome. What does that mean, and how is that put in context. So, I think the combination of that. How frequently do WES results cause harm to family relationships?

Cost per diagnosis, depending on the pathway that includes WES testing, cost for additional diagnosis compared to a pathway with WES in it at some point, and what is the cost-effectiveness overall of testing with WES?

In terms of the different codes, there are three ways in which WES is paid for at the Health Care Authority. It's either at the individual testing level, and that's the 81415; at the individual parent and sibling, or the trio WES level, 81416; and then a repeat test for an individual is 81417.

Looking at utilization over the last three years, you can see . . .

Gregory Brown: Can I interrupt you? Theresa, I'm sorry. The last one?

Charissa Fotinos: Yes.

Gregory Brown: 'Cuz one of the things the report talked about is not so much . . . I mean, if you've already done whole exome sequencing, don't you have all the data?

Charissa Fotinos: You do, but what happens, and our expert will speak to this later is, this is a fascinating and extraordinarily complicated field, but often as new variants are identified and the findings are updated, and they become associated with conditions, what might not have been diagnosable two years ago, in two years there is now an association and a diagnosis for that. So, it's not repeating the genetic sequence. It's re-running it through the new algorithm to reveal more information.

Gregory Brown: OK. And presumably, that's relatively inexpensive, or not?

Charissa Fotinos: There's a slide coming up that shows the cost difference. It is absolutely less expensive than . . . well, we pay much less than the first one. I don't know how expensive it is.

So, looking at utilization, you can see that we've done in 2018 about 184 WES tests on 91 patients, and the cost has increased, but if you look at the relative cost per the number done, you can see that the cost, overall, has decreased over each of the years.

An interesting trend in the 81415, the individual testing versus the parent or sibling, the trio WES testing, you can see as the years have gone, they've been about equal and slightly more numbers of family members tested as well, over that time. One of the things that is interesting that I didn't include in the slide, but in 2015, a good chunk of the people who were being tested were over 23. In 2018, the vast majority of people who were tested were less than, I believe, 12 years old. So, there's been a shift in how the test is being used.

These are some of . . . and I would say on that last slide, these were for Medicaid fee for service and managed care, did not reflect the public employee plan, because there were too few tests to show and have any risk of identification of folks, but these are some of the diagnoses that accompanied the request for WES testing. I won't go through all of them, but you can see autistic disorder is one, unspecified convulsions, short stature, microcephaly, delayed milestones. These are just 105 of those tested.

Here are the rates that Medicaid pays for the testing. The 81415, which is the individual testing, is \$4500. For the trio, it's \$11,000. That's per test, so that would be \$11,000 times 3. Then the repeat testing is \$300. The good news is . . . oh, it didn't show up on this slide. That's unfortunate. The 81416 starting in November is now the same price as the 81415. The trio is now the same as the individual. For some reason, Medicare had it at a much higher rate, but we were able to talk with our rate folks, and

they said, yes. We can adjust that to be the same price. So, we do the \$4500.

Current coverage strategies, PEBB and UMP is considered investigational. Medicaid does currently cover WES testing with prior authorization. Labor and Industries does not cover it. We did not reach out to the Department of Corrections.

What do other payers cover? Regence determines that WES is investigational for all indications. They specify clearly which ones. If it is considered medically necessary for the evaluation of unexplained congenital or neurodevelopmental disorders in children less than 21 when the criteria are met. There are a number. Cigna, similarly, is considered medically necessary when a number of criteria are met, and the test is ordered by one of their named specialists.

CMS really focuses WES testing on cancer and related to either recurrent, relapses, refractory, metastatic, or advanced stage cancer. They spell out when the testing can be done in relation to it prior having been done.

Sheila Rege: You said Aetna has named specialists that they authorize?

Charissa Fotinos: They don't name them, but there is a network of people that they . . . sort of genetic counselors that they . . . centers of excellence. You have to go to our specialist if you're going to order this test. Or not theirs but identified ones.

Then, just to finish the CMS, they say that it has to be in a certified lab. There has to be an FDA approval for the clearance as a companion. It's largely around tumor identification and response. So, you're going to hear from the evidence vendor, the path by which they came up with their levels of evidence, and the terms of certainty around the clinical utility, which is deemed to be very low, health outcomes really not enough to determine whether they are improved. Safety, low level of evidence. Then, cost-effectiveness, very low quality of evidence in terms of ability to make determinations. So, were this a normal Health Technology Assessment looking at those, we would look at that and say we're not going to cover this, because the evidence really doesn't support a broad coverage of this; however, given the evidence and, as [inaudible] it is for me to say [inaudible] and decide for a minute, there are other considerations when thinking about this test. So, what are those considerations? There are currently an array of costly diagnostic tests that are used in strategies to identify presumed genetic conditions really that

don't have great diagnostic yield. And you'll hear from RTI exactly what those yields are.

This is a . . . I apologize you're not able to see it very well, but this is sort of a current testing pathway for how often a genetic diagnosis is pursued. I cannot see to read that, but essentially, certain tests may be done, whether it's a single gene, a gene panel, a FISH test, a chromosomal analysis. You'll see those up in the top half. Often, there is not a yield or a diagnosis made. Chromosomal microarray may be included in that. And when you add those different tests up in whatever order you might do them, it's about \$5000. Instead, if on the lower half, if those are all not diagnostic, then you can proceed with the WES knowing that WES, itself, is \$4500 is the yield of a WES alone in the clinical testing pathway high enough or substantial enough to obviate the need for those other tests. So, that's one of the considerations, I think, the agency medical directors had when we put this forward. Yes?

Mika Sinanan: Can I ask a question about that last part? What you're implying is that the [inaudible] is conclusive of all the [inaudible].

Charissa Fotinos: It can, yeah. There are . . . And I will let the experts, but right. There are some things that the WES is not able to identify that those other tests can, just in the way it reads things is my understanding. I don't know, and maybe our researchers can tell us the gap in difference, but overall, the diagnostic yield of the WES is superior to those others, certainly alone, and perhaps in combination. I see a slight nod. So, yeah. So, it can't identify everything, but it identifies as much as those do. There are some gaps in terms of it can miss long sequences of changes, I think. So, there are some gaps, but the point of this slide is right now, when the sort of diagnostic odyssey is happening, people will go through all of these tests. They might not have anything. They might not have anything. In comparison to those, the yield of WES is higher. Did you want to say something, just for clarification?

Amy Yuen: I was going to say there is a number of different things that a WES can miss. It can miss trinucleotide repeat disorders. It can miss changes that are in the intergenic areas. If the WES does not include the mitochondrial genome, it won't detect changes in the mitochondrial genome. So, there are a number of different mechanisms that a WES could miss.

Female: Would those other tests reveal those?

Amy Yuen: You could do possibly single gene or a specific, but you'd have to know what you're looking for.

Charissa Fotinos: So, it's sort of a fishing expedition in a way for the moment? Basically, like I said, there is currently an array of diagnostic tests and strategies. I think this slide was out of order here.

The field is complex, and the interpretation of findings is nuance. I was remarking to Kevin this morning, when I was in college, I loved genetics, because it was just of the fly, right? And there was recessive, chromosomal dominant. I had to review the definitions every time I read them. It's extraordinarily complex and nuance. So, I just want to kind of point out some of the thinking. This is just in terms of what you could order. You can order a single gene, as you can see up there, whether it's the cystic fibrosis gene or others. You can order a gene panel, particularly good for muscular dystrophy panels, cardiomyopathy, epilepsy. You can look at an exome testing, which you can see some of the indications, autism, general diarrhea, Zellweger syndrome. Then, the genome, which includes the enterons and exomes in the mitochondrial DNA, and you can add to that. So, in order to figure out which of these might make sense, you have to be a geneticist or someone familiar with the phenotypes that go with these different conditions and to know what you're looking at and when you might need more information than you can get from the standard testing.

Not only is there a lot of variation in terms of how people present, but these tests are complicated. The more steps you have, the more likelihood there is for variation. This is just sort of a sequence of how whole exome capture and sequencing is performed. In each of these levels on the right, there is a database it has to be checked against. Those databases can differ. There are algorithms that run that determine how to interpret that based on what the sequencing reads. There are statistics that have to be put in to say, is this variant at the rate we're seeing it more or less than what we would expect in the regular genome. There are multiple places in which someone who reviews the test needs to understand, is this . . . what database are they using? How many reads were done at what percentage error. I think that what we've seen in Medicaid is, we have people who are ordering this test for kids who are developmentally delayed, or behind in school. Doctors should not order things that we don't understand, I think, and I think this is something that is extraordinarily complex and requires a lot of nuance to understand the results. Even though they're given to you as either here is a potentially ethnogenic or a pathogenic variant, I think you still have to look under the cover to see what all is involved. Then, there is the grading of variants. This is an evolving field. So, you can have a benign variant with strong evidence to support that determination. Or you can have a pathogenic variant with strong or very strong evidence to support that. This is fine

print. I don't even understand the words in these boxes that tell you how you know which is which. Again, this is complicated. There's a bright future for geneticists. Let me say that.

As more people are tested, the knowledge of different variants and their significance across different populations will expand. I think one of the things that would come up periodically in the reading is that these are largely . . . the genomes that serve as databases are often largely white populations. There is regional variation. There is gender variation. There is racial and ethnic variation. And this is a universe to really interpret findings within the context of those. The other consideration is that there are, now, 59 medically actionable secondary findings that might occur, as identified by the American College of Medical Genetics. That seems to be if there is one of those identified, important to identify early and/or prevent the development of breast cancer or another medically actionable.

So, this is the list that we looked at before. Thinking about it again, in terms of Medicaid, some of these are crossed out, but essentially, in terms of thinking about it specifically toward the Medicaid population, really the second bullet, explaining phenotypic abnormalities of unknown etiology, that's important. Enabling more appropriate treatment is important. Enabling patients to benefit either from existing or emerging treatment trials if it happens to be in concurrence with that, really not appropriate in the agency medical directors' determination for prenatal or preimplantation diagnoses, and there are not any plans that cover it for that, even in those that do. Enabling predictive testing for late onset disorders, really not appropriate, unless there are some syndromic findings to guess there may be, or a family history of that. If you're looking for late onset disorders, there may be more specific tests for that. Testing for family members with some caveats not really appropriate for Medicaid, and carrier testing again, sort of a more vague area.

So, in summary, we recommend that WES be covered with the conditions when there are multiple congenital abnormalities affecting unrelated organs systems and a single gene test or gene panels either have not or are not expected to yield a diagnosis based on clinical presentation. The constellation of clinical findings could be found in more than one genetically associated condition. The test is recommended by, or as a result of a documented consultation with a medical geneticist or board certified genetic counselor, and genetic counseling is provided before and after the findings are known and there is no other causative circumstance, whether that be environmental exposure, injury, infection that can explain the symptoms, and one or more of the following were expected to occur

once a diagnosis is reached. That medication or other treatments are started or discontinued. Contraindicated care is discontinued. Palliative care is initiated, and/or care is withdrawn. So, those are sort of the, the broad, uh, recommendations. Or, and this is, this is sort of a little bit trickier piece, and I may not have the . . . we may not have the language right, but when there are at least two of the following present, either autism, global developmental delay, intellectual disability, complex behavioral disorders, or severe neuropsychiatric symptoms. There are, I can't remember, but there are close to or well over 100 variants that have been associated with autism, none of which are necessarily actionable. So, we've been seeing a lot of requests for, again, testing to define what genetic variant is leading to global developmental delay or autism. So, either alone or together, because we're not able to intervene in a different way knowing that genetic abnormality, we don't find those alone to be . . . we don't recommend that those alone be cause for testing. An abnormality effecting at least one other organ system and not described in the previous bullet. Family history is strongly suggested. A period of unexplained developmental regression that's unrelated to either autism or epilepsy, and biochemical findings suggestive of an inborn error of metabolism. So, any two of those would also be an indication for testing.

Whole exome sequencing is not covered, as I mentioned, for autism, developmental delay, intellectual disability, complex behavioral disorders, or severe neuropsychiatric symptoms alone or in combination with themselves. Asymptomatic first-degree relatives of the person receiving the results, unless there is a medically actionable secondary finding that was identified, and I wanted to be clear. This does not exclude the use of trio-testing. So, either siblings or parents do need to have their testing done to determine whether or not a variant in the proband or the person being tested is, in fact, familial or not. So, that is not meant to exclude that testing. Not done to reduce diagnostic uncertainty. Not looking for carrier testing of 'at risk' relatives, prenatal, or preimplantation planning, and not covered for future pregnancy counseling for a parent or a sibling of a child that has had a genetic mutation identified, unless that is heritable, and the birth parent is covered by a Health Care Authority plan, again knowing that people over time come on and off different insurances.

So, that is a lot, and it's complicated, but those are our recommendations. I'd be happy to answer any questions, if there are any. Yes?

Laurie Mischley: The only question I have has to do with the increase. 2015, it was almost 1 exome sequence per unique patient. And then there's almost a 2:1 ratio now?

- Charissa Fotinos: And I think that's because if you look at, I'm sorry. I think that's because the increase in the parent and sibling testing that goes along with it. So, it . . . looking at our numbers, and I apologize. I didn't include that slide, but let me get back to it here. If you look . . . when it started, the vast majority of tests that were done were on an individual. So, there would be one. If you look, uh, there have been more siblings and parents tested. That still falls under that, that same person. So, you'll have more tests of different people for that same person.
- Laurie Mischley: OK.
- Male: Do we know right now, which types of practitioners are ordering these tests? Is it mostly geneticists or other . . .
- Charissa Fotinos: Sadly, we have a bunch of pediatricians and other people ordering them. Dr. Johnson is not here. She is the person who has to stamp all these down. And it's really not . . . part of our intent of this is to really have the specialists who are in the best position to know if it's appropriate and interpret it, order it. So, we want to be more explicit in our recommendations around that, but right now, we have pediatricians. We have neurologists who are ordering it for different things. So, it's not, and again, it's a new test. It's cool. How cool is it to know someone's genome, but I don't know what to do with that. So, I think it's just kind of the excitement. We can do this, but then I don't really understand it well enough to be doing it.
- Gregory Brown: So, in light of that, I would have to say this is the most coverage recommendation I've seen in my years on the committee. So, is another when you guys as the medical directors talk about this also is, should we be shifting to saying who can order the test. So, rather . . .
- Charissa Fotinos: That is the recommendation.
- Gregory Brown: . . . right. So, rather than trying to be prescriptive with all these recommendations, say if a medical geneticist can order them for appropriate conditions, so that you don't have pediatricians or general internists ordering because they wanna know.
- Charissa Fotinos: Sure. I think, and I would like our consultant to weight in. I think we have also had genetic counselors who have ordered tests without perhaps the breadth of knowledge to order them appropriately in this case. Again, I wish Dr. Johnson were here. So, if we are told that if you have X border degree, yes. You're going to order appropriately all the time, but this is pretty consistent with all of the other insurers who cover it, really being

this prescriptive, because this is where what evidence we have suggests that there is a benefit. So, I think that's . . .

Gregory Brown: No, fair enough. Thank you.

Amy Yuen: I would say this is the one genetic test at our hospital that we've asked our laboratory to only send it out if it's been ordered by genetics department.

Female: Could you speak up a little bit?

Amy Yuen: So, I was saying, at my hospital, at Mary Bridge, this is the one genetic test that we've asked our laboratory to only send it through if it's been ordered by the genetics department. We tried to be very open and unrestrictive of the order patterns of our medical group, but with this one, there's so much complexity into knowing was it the right test? Has the family had the appropriate counseling? Do they understand what the test is that's being ordered? Do they understand about secondary findings? Have they had the opportunity to decide? Do they want secondary findings? Do they know what to expect from the test? And then, even from the basic standpoints of has the right order form been filled in? Has the right consent form been provided to the laboratory? So, at Mary Bridge, we have made for exome testing, it can only be sent out if genetics has ordered it.

Charissa Fotinos: And that's the other consideration we have is, is this a center of excellence type review? And if so, are there enough of those in the state to be able to handle whatever requests might come in. I don't know the answer to that, but that was another consideration while we were talking.

Gregory Brown: Thank you.

Charissa Fotinos: Mm-hmm.

Janna Friedly: Can I ask a question about followup? Genetic counseling, is that currently covered? Do we have data on historically whether the people who have been ordering this have actually been using genetic counseling. I assume that's billed separately so you can track whether or not they've had pre-testing, genetic counseling.

Charissa Fotinos: Do you recall from your Medicaid days if genetic counseling is covered? OK. We're checking to see if it's covered. I believe it is. When we did . . . we should . . . we can and will track the association of when this ordered if genetic counseling occurred or not. It's a great question, and we did not . . .

- Janna Friedly: And availability in terms of access of genetic, if you were to move forward with these recommendations. Is there appropriate access to genetic counseling. I assume if a geneticist is ordering this at Mary Bridge, obviously there is counseling available, but in the community at large is that true? Is there . . .
- Charissa Fotinos: And one of the other questions that we had for the consultant is that it seems like in . . . and I don't . . . that this might be amenable to a TeleHealth visit via video, if there's enough information at the time. So, in terms of geographic access, it seems like we could help support that TeleHealth kind of perspective, if that were appropriate in this setting.
- Amy Yuen: The pre- and post-test counseling would be very amenable to a telemedicine situation.
- Janna Friedly: Also, when you're looking at the costs of this, this is looking at just those individual costs, but it's not really looking at sort of the pre and post costs associated with it.
- Charissa Fotinos: Right. And we can get you both if those are covered. Dr. Transue has [inaudible].
- Emily Transue: I was just gonna say, we can check that for UMP as well, remembering that everything that happens in this committee applies to UMP, as well as Medicaid.
- Charissa Fotinos: So, we can have those for you by this afternoon. Those are good questions. OK. So, it is covered? Then, we can check on UMP and see what those rates might add to this.
- Mika Sinanan: My question is, you made the comment that as much as you dislike it, you discard the information in a transition from what you think the evidence supports and then make recommendations, but you didn't say why you gave recommendations different from what the data supports.
- Charissa Fotinos: I apologize. I was unclear. I think in my mind, and that was somewhat of an iffy comment on my part. I do . . . I have a special interest in evidence-based medicine. So, I like it to be really cut and dried, and it's usually not. I think that this is different, because we've already got families who are looking to have a diagnosis. And we've got different places where they touch the system where different tests may be done, and when you add them up, they are not particular high yield. And they are expensive or as or more expensive in combination than this is. So, the diagnostic yield of

WES as we will hear, is better than chromosomal microarray. If you know you're looking at something, and you get a single gene test or a panel, and that's confirmed, that's good, but if you don't know what you're looking for, you can do a lot of panels and cost a lot of money. So, in terms of efficiency and sort of reasonableness in terms of us paying for whatever comes across, this makes more sense from a clinical perspective. If you're going to test something, this makes the most sense to test. The validity of the results, the utility of the results, we'll hear from our evidence vendor how that weighs against this, but from our perspective, we're paying for a lot in this area. Given that, is this a good enough test to warrant saying you can start here in the appropriate circumstances when determined by the appropriate person, because the yield is going to be higher than you just searching for stuff. Does that make sense?

Mika Sinanan: Yes. Thank you. And I presume that all of the other specific studies are covered.

Charissa Fotinos: Yes.

Mika Sinanan: OK.

Charissa Fotinos: And those are our rates for those that I put up there.

Gregory Brown: And if I can paraphrase, I think the report said that the sooner it's used, the more cost-effective it is, which is, I think, kind of what you're saying.

Charissa Fotinos: And the literature doesn't show that, but in terms of Medicaid, and I didn't price it for UMP, but we can sort of look at that, I don't know if that same is true on the UMP side. I would assume, those tests are . . . we pay way less than anybody. So, if that's what we pay, I suspect commercial payers pay more for those tests in combination. So, I suspect that it would, from a cost standpoint still be more efficient to do this.

Gregory Brown: So, I guess the other thing that I don't know that's explicitly in there, but it's almost effectively in there is, are you saying this is just for kids, not for adults?

Charissa Fotinos: I was hoping you would decide that. The yield is higher the younger that the person who is tested is, and I don't recall. I think it's 40-plus percent in infants and toddlers and goes down per adults. I think that we didn't make an explicit recommendation. Right now, we don't have an age limitation. I don't know enough, and again here our expert can help us. I don't know the yield in people, as they age if something hasn't already been determined. So, I would not have a problem if the committee says

this is up to a certain age. We didn't specify it. I certainly think that the evidence would suggest testing younger folks is probably more utility. I don't know if you want to [inaudible].

Amy Yuen: I don't think there has been a study clearly showing a . . . looking at a breakdown by age. In general, many more of the patients that I test for this are children, but occasionally there is an adult for whom it's appropriate. Sometimes, it's an adult who had a congenital onset of symptoms and just never had the opportunity to have the evaluation when they were younger. Or, sometimes, it's an adult who has some type of neurodegenerative or regressive disorder that we can't, after evaluating them and doing appropriate tests that we may have thought of, we can't find a diagnosis for them. And if they are degenerating, it's appropriate in those situations.

Gregory Brown: Thank you.

Sheila Rege: Just so it's discussed, I wanted to figure out, depending on what recommendations we make about the whole exome sequencing, or if in your opinion it includes or excludes the FISH testing, which is completely different, the karyotype testing, which is also . . . do you think it includes either of those? Or would it be already discussed, the chromosomal microarray analysis.

Charissa Fotinos: So, what I would say is that in terms of, I am just a family doctor. In terms of defining circumstances in which this would not be enough, another test would be appropriate. That's partly why we said it's got to be a genetic clinician that orders this to understand. Maybe you can speak to when one is appropriate versus the other, or when you might need them in combination. I don't know enough to know that.

Amy Yuen: So, the exome technology has improved significantly over the years. Many of the exomes that are available now will pick up what's called copy number variants. So, if there is a gain or a loss in the chromosomes, you may be able to detect that on the WES. It will not be able to tell you anything about a structural rearrangement in the chromosomes. So, depending on the patient's situation, sometimes it may be more cost-effective to do the chromosome array or a particular FISH if you suspected a certain region very highly to do that first. Then, if that is not diagnostic to move onto the WES.

Sheila Rege: Only because of clinical pathways process, the patient with breast cancer could be the surgical oncologist or the medical oncologist ordering the FISH to get the information. So, we want to, if we are making a decision and

including that, we need to make sure that we're aware of those special circumstances before accepted. So, that should either be excluded or . . .

Charissa Fotinos: I see this as standalone. Any test that you would currently order to do an oncological treatment or anything, that would be unchanged. This is really a subset of circumstances under which this test would be appropriate, and it would not change how things are currently done.

Sheila Rege: Because that has enough data in there, in the literature.

Charissa Fotinos: That I . . .

Sheila Rege: So, that's, OK. It's not . . .

Charissa Fotinos: . . . I don't know that. That's a different question.

Mika Sinanan: I have sort of a followup question before our expert . . . before the RTA group. Perhaps, you can help answer this. If you took the same sample and gave it to multiple labs, do you get different answers? Do you have to choose the lab you send it to?

Amy Yuen: That's a very good question. Usually, we don't send out testing to multiple different labs. So, I don't know how it would turn out, but we do very carefully choose the laboratory that we're going to send it to, based on a number of factors. Usually, our previous experience with that laboratory of getting back results, their cost. There are some differences between what WES tests will include at different laboratories. So, many of them now have the copy number variation, but not all do. Some will include a mitochondrial genome, but not all do. Some will include specific testing to look for something called unique parental disomy where two chromosomes come from the same parent instead of one from each. Some laboratories provide free re-analysis in the future, which can be an enormous benefit if you get back a negative test knowing that at a future point, at no charge, I can tell the laboratory to reanalyze the data. Most laboratories will only do that once, but some laboratories are now moving to unlimited reanalysis. So, if you reanalyze in a year, and it's negative, you can go back in another year and another year. So, there's different levels of value that I can get from different laboratories.

Mika Sinanan: So, if the prices are different, it's potentially true that if Medicaid sets a value, some labs will accept that rate and others will not. Is that correct?

Amy Yuen: And some laboratories may even be charging less than the rate that you've set it at. There's an enormous range on the pricing, and one of the

challenges we found is some laboratories are very upfront and will tell you the price. They'll have it on the website, and I can call and I get the price, and I know that is the price whether they are dealing with the insurance provider or whether they're dealing with the hospital, or whether they're dealing with the family. The price is the price. Then, there are some other laboratories that have actually refused to tell us what the actual price is that they're going to bill. So, this is something we also take into account when we're choosing a laboratory. So, I don't want to choose a laboratory that won't tell me what they're going to charge you. I want a laboratory that tells me very clearly this is the price.

Tony Yen: I just have a question about the validity of these results. Don't different laboratories have different reference genomes? Is that accurate or not?

Charissa Fotinos: They should be all using standard reference sequences. On the report, typically they will not list it for an exome, because there will be so many of them, but if you're sequencing a gene, they will tell you, this is reference ID, and they will give you the number for it. So, if you have an exome that comes back positive, you can tell the laboratory, OK, what reference ID is this one. And they should all be using a standard reference.

Tony Yen: But they should all be using the same reference genome?

Charissa Fotinos: Yes.

Tony Yen: But then, each of their algorithms, in terms of matching on sequencing are probably slightly different?

Charissa Fotinos: They may have proprietary algorithms.

Tony Yen: OK.

John Bramhall: So, from a practical standpoint, a family comes to you for counseling about, let's say, autism. It seems to me that that's a pretty substantial problem that people face. My question is, is it then . . . would it then be conventional for you to, in that setting, to recommend an array genetic testing for the possibility of finding a mutation that would be relevant to the disease? Is that something that you would typically get involved with?

Amy Yuen: Yes. And that would be a very common starting point for an individual with autism. When they come into the clinic, we would take their history, examine them, see if a particular syndrome or gene appeared to match based on their examination. Then, if not, typically the first step would be looking at their chromosome array.

- John Bramhall: Alright. So, that was my followup question. If you found no match in the conventional array, it wouldn't be automatic, but you would then recommend a WES?
- Amy Yuen: Not necessarily. So, once we had obtained that array and it came back negative, we would then speak with the family. I think a lot would go into the family's preference on how much testing they want to proceed with, and how severe the patient's phenotype was. So, if this individual had a milder autism, we might not press on with more testing, but if the family has a child who is profoundly autistic, nonverbal, maybe with other associated medical issues, perhaps they have epilepsy, then we'd say, OK. In this case, this appears appropriate to keep moving on. Let's look at the exome.
- John Bramhall: I'm talking a research standpoint, not clinical practice, but from a research standpoint, a person presenting with significant signs and symptoms of let's say autism who is negative for the conventional panel, from a research standpoint, the next step might, seems to me the next step would be exome analysis so that then data can be used to contribute to the development of a more advanced panel. Is that, is that a reasonable sort of description of the pathway?
- Amy Yuen: Yes. Many research groups looking at that, they move onto an exome.
- John Bramhall: So, your panel becomes more sophisticated the more times these are tested?
- Amy Yuen: The more individuals that you test, the better you understand the range of genetic variants, which can also then inform the development of better panels.
- Gregory Brown: We better move along. So, next we have scheduled an open public comments. We have two individuals?
- Josh Morse: So, there are two who signed up in advance to speak today. And nobody has signed up on the day of for comments. So, the first sign up is, sorry? Sarah [inaudible]. I got it all wrong. So, I'm sorry.
- Gregory Brown: So, we ask all public speakers if you could give us your background and who you're representing, and if you have any conflicts.

Sarah Clowes Candadai: I'm Sarah Clowes Candadai. I'm a genetic counselor with the Seattle Children's Hospital Department of Laboratories. Seattle Children's lab doesn't actually perform any exome testing in our own lab, but we have a lot of experience coordinating genetic testing for our patients across the hospital. That's why I wanted to share a little bit about today. So, I am currently the Chair of our exome sequencing committee through Seattle Children's Hospital. The purpose of that committee is to ensure appropriate use of testing across all of our patients at Seattle Children's. Similar to Dr. Yuen's statement about Multicare privileging exomes to only genetics, the genetics department, we ensure that all recommendations for exome sequencing are at least reviewed by geneticists, genetic counselors, and laboratorians with varied expertise in molecular genetic testing, including exomes. So, the committee, itself, includes medical geneticists, genetic counselors, and laboratorians as I said, and one of the most impactful ways we enter appropriate use of testing is to review recommendations for exome sequencing from non-genetics providers. So, while we don't have . . . unfortunately, we don't have the access for every child who should be eligible for exome sequencing when it's appropriate to be seen in person by a geneticist. We are at least able to review the clinical history, family history, and other records electronically to make sure there is consensus among our genetics group for when exome sequencing is appropriate for patients who aren't able to be seen in person in the genetics clinics. That type of review, we feel, is really impactful to improving the safety of testing, as was mentioned. With that review, we're able to interpret genetic counseling, as provided by genetic counselors. There is much greater access to genetic counseling than to a genetics in person visit. So, we can have our geneticist review, make sure that the testing is appropriate, and then provide genetic counseling, both pre and post tests when applicable. Just as a comment, the way we typically recommend trio-exome sequence be performed, just because it is a much higher yield in general. So, that's billed with 81415 and then 81416 x2 for each parent typically. I just want to thank the committee for hearing exome sequencing. We have found, over the years we've been providing exome sequencing, that it has been very impactful to our patients. It does change their care. It ends the diagnostic odyssey. Even when negative, there are opportunities for reevaluation. It cuts the amount of genetic testing down that's needed, as was also mentioned. Instead of doing onesy twosey panels over time for patients, we are able to do exome sequencing, and that's kind of the last tier test that's recommended. So, the sooner we can do exome sequencing for patients, the sooner we are able to say, OK. That's all we've been able to do for now, but here's our plan moving forward to continue to assess if there is a genetic etiology for you and the family as a whole. So, thank you for hearing those comments.

Gregory Brown: Thank you.

Female: Can I just ask a question? Is that OK? Can I just ask a clarifying question? So, if a recommendation were made by this committee to limit this testing only ordering of tests to geneticists, how would that impact access at Seattle Children's, for example. It sounded like that might be a bottleneck.

Sarah Clowes Candadai: I think, yes. I think the access is poor to geneticists in person. I do feel that, the committee often either approves the exome based on the clinical features. Or they will sometimes recommend being seen in a genetics clinic for further evaluation. So, I think even just the kind of electronic review, even though it's not an in-person consultation, it is documented. We do have forms that are completed that could be shared with payers. I think at least that review is impactful, even if, and is less of a bottleneck, potentially, than actually having to schedule the patient to be seen. Does that answer your question?

Female: Yep, that's, thank you.

Gregory Brown: Then, we have a second person.

Josh Morse: Yes. The second person signed up is Jessie Conta. Thank you. And I didn't mention before, but we typically limit the comments to about three minutes in the event that we have many comments. So, there aren't that many today, but if you could limit to maybe four minutes, it would be appreciated.

Jessie Conta: I'll keep it concise.

Josh Morse: Thank you.

Jessie Conta: So, my name is Jessie Conta. I am also a genetic counselor. I am here representing PLUGS, but I do work at Seattle Children's Hospital, and PLUGS is a nonprofit within the Department of Labs at Seattle Children's. It's focused on laboratory stewardship. So, Sarah and I are colleagues. We see families together at Seattle Children's and have that experience, but in my three minutes, what I wanted to just share was, from PLUGS perspective, just thank you for reviewing this topic. I think it's a really important review. We appreciate that this is a forward-thinking committee, and for PLUGS, what our goal is, is to ensure that patients get access to medically appropriate tests, and that we're able to reduce waste. So, what Sarah described as having the right expert review tests, we know about a third of the time, genetic tests are ordered in error, particularly when a genetics provider is not involved. So, having a right expert review

that really does improve the diagnostic yield and preserves healthcare dollars the way we would want them to. So, PLUGS has created a coverage policy for exome sequencing. We make them freely available, because we want to make sure that that evidence is out there. It's been adopted by many payers. Aetna was mentioned. So, if you look at their criteria, that's the specific coverage criteria that we recommended. It's limited. So, ours says less than 21 years of age would be the appropriate use for this to ensure access to the people who need it most, even though to Dr. Yuen's point, there are certainly patients who, if they had had that opportunity when they were younger, it would make an impact for them. So, in our written feedback, we did provide a copy of that policy, and it's freely available. The second part I just wanted to highlight on was related to cost. So, I think we've already pointed that out that the rate for 814016, for that trio, is inappropriately high from CMS. So, it's \$11,000. It really should be more on the order of \$1000. It's, like, a decimal point off, and trios are very impactful. So, I think if you were to set your rates, it sounds like that's the way it would be. That's very appropriate to not pay more than that \$4000 or \$5000 for a trio. There just wouldn't be access for the patients that really need it. That's really all I wanted to say. Again, thank you for the thoughtful review.

Gregory Brown: Thank you. Then, is our phone line unmuted? OK. This is Greg Brown. I am Chair of the Health Technology Clinical Committee. We are reviewing whole exome sequencing today, and we are wondering if anybody is on the line and would like to make a public comment? OK. It does not sound like we do. So, I actually may take a Chair's prerogative. I would say, let's do our report before we take our break. We kind of got a late start. So, instead of one hour and three hours, let's do two and two hour with a break in the middle. Anybody object to that change in agenda a little bit? OK. Then, I think we are . . . if you want to meet at the line again, we are ready for our vendor presentation.

Nedra Whitehead: Good morning. I'm Nedra Whitehead. Some of you may remember me from the chromosomal microarray presentation a couple years ago. I'm with RTI International, and I am please today to discuss our Health Technology Assessment of whole exome sequencing.

Female: Nedra, just a moment. I'm sorry. I have brought up the wrong presentation. There, yeah.

Nedra Whitehead: Thank you. OK. so, this is just a brief overview of my presentation. Contextual questions are often discussed last, but in this case, it's so important to understanding the overall context, I'm going to discuss the contextual question on diagnostic yield first.

As was alluded to, it's a complex topic with a lot of words and phrases you may not have heard before. Here are some definitions you may want to look at. So, variant classification was discussed earlier. Variants of unknown significance are those that you can't . . . you don't have enough evidence to know whether or not they cause the disease. Whereas, causal is one that you've got strong evidence that it is the cause for disease. Clinical validity of sequencing is about the accuracy of the classification, not the accuracy of the actual laboratory sequencing. Secondary findings are on identification of a DNA variant that causes a disease. It's different but isn't consistent with the phenotype that's being presented. It's a different disease altogether.

As [inaudible] mentioned, we did a review a couple years ago on chromosomal microarray to diagnose chromosomal abnormalities in children who presented, and that was presented January of 2018. The original scope of that review included whole exome sequencing, but since that time, WES was really not good at detecting copy number variants. The actual eligible evidence was low. It underestimated the efficacy of WES and did not provide enough evidence to make a policy determination. So, we are doing this strictly focused on WES.

This gets to some extent to the, the [inaudible] that were brought up earlier. Genomic changes range in size from whole chromosomes being duplicated or missing to single variant changes in a single nucleotide. The severity of the phenotype that's presented does not necessarily correlate with the size of the change. The technology that identifies things does, so that karyotype can identify large whole chromosome changes or large portions of chromosomes that are moved, deleted, or duplicated. Chromosomal microarray can identify changes across the genome that are as small as 30,000 base pairs. Sequencing was best at small changes, as little as the single nucleotide changes and is actually less sensitive to the larger changes, although I said two years ago that at this point it was a bioinformatics that was the problem with being able to use WES to identify chromosomal microarray, it's caught up. At this point, as Dr. Yuen said earlier, WES will identify many copy number variants. Not all of them.

This is a schematic of how WES happens. You take the genome. You cut it up into lots and lots of copies of the genome, cut up into lots of little pieces. You use probes to pull out the pieces that are actually part of the genes that cover for [inaudible] genes. Then you seek those parts of the genome only. You align them to a reference sequence to be able to interpret what that patient's sequence is. For those parts of the genome, the code for protein.

Then, you do bioinformatics, many steps of bioinformatics. First, you use the bioinformatics to actually interpret what your laboratory has told you, what your sequencing machine told you about what those base pairs are to align them to the reference genome. Then, to figure out of the usual around 20,000 variants that show up in any individual exome, which one of those are actually telling you something about the disease the patient has? You filter on the commonness of the variant from public databases, which genes they're in, and what those genes do, and how variants in that gene are usually inherited, and what's your pedigree and your family information look like, and what kind of phenotype you're expected to have. Then, you come up with a few variants that may be causal.

Then, you look for the evidence in the literature in predictive algorithms to see if that variant is likely to cause disease or has been shown to cause that disease in other patients. From that, you put out a report that says this is causal. This is consistent with the patient having the disease. This is a variant that might be consistent with the patient having the disease. We didn't find any variants that would be expected to cause this disease.

I got more than 6000. That's the last time somebody actually scraped the online [inaudible] and inheritance in man and counted how many genetic diseases there were. I've seen a number as high as 10,000 different human genetic diseases that collectively effect as many as 1:17 individuals. WES can identify many of these diseases. It's commonly used when a patient has an unrecognized phenotype that's suspected of being genetic, has a phenotype that's consistent with a lot of different genetic disorders, or shows features of more than one genetic disease.

I thought it might be helpful to actually look at two theoretical examples of how it might be used. In example one, you have two siblings that present with very similar symptoms. Pedigrees consistent with an autosomal recessive disorder, the symptoms aren't really specific to any given disorder or a defined group of disorders. So, there's no clear single gene or gene panel that should be tested that could tell you what this is. You see, they have hypotonia, oculogyric crises where the eyes kind of move back and freeze in their head, developmental delay. Onset is usually in infancy. Other than these two siblings, you don't have any other family history. Differential diagnoses are neurotransmitter deficiency. Kids are often misdiagnosed, sometimes with cerebral palsy or other kinds of more general neurological issues, and the genetic testing management and treatment options differ. Some of the genetic defects in this pathway can be treated with existing pharmaceuticals. This happens to be taken from one of my other projects. It is L-amino acid decarboxylase deficiency. It

has no treatment on the market. The next is a 29-year-old woman with endometrial cancer who has a family history that includes multiple cases of different cancers in young adults. The differential diagnoses here are a whole variety of inherited cancer syndromes, genetic testing, which cancers are at high risk in the family, the management and treatment options differ and there are multi-gene hereditary cancer panels that contain as many as 86 different high and moderate penetrance genes that are available. The choice of those could very easily come down to what's a comparative diagnostic yield? And what's the cost of the panel versus the cost of WES?

Mika Sinanan: Can I ask a question? So, take your first example. Suppose the phenotype is very clear. How often, if you know, is confirmation sought? In other words, well, it looks like this, but let's do a genetic test to confirm it kind of question. And if so, would that include WES? Or is it always more targeted?

Nedra Whitehead: That is probably a better question for Dr. Yuen. We didn't actually look at that in our evidence, and it's been a very long time, since I actually did clinical genetic tests.

Amy Yuen: So, for this example, I would not go to WES first, because there's a biochemical marker for that condition. Oculogyric crisis is a relatively specific finding. So, if I saw that and I thought about ADD, I would do the biochemical marker first. I could get that back pretty quickly, see am I on the right track. Then, I can do a single gene test and confirm it. Or, no. I'm not on the right track. I gotta go broader. So, then exome makes sense. Gene therapy is coming out for this in February. So, if this were the situation, I would say, oh, I really do need to diagnose this child quickly, because in this situation with gene therapy coming out, the indications from the trials are that the sooner you treat someone the better. Children who are already symptomatic actually improve, and they improve more the earlier they are treated. So, in situations like that, I would go with specific testing. Then, if that was not the correct diagnosis, then I would go out to the exome.

Mika Sinanan: Thank you. That's very helpful. So, virtually, as often as possible, even with a specific clinical diagnosis or laboratory diagnosis, you will take this step of doing the genetic testing to confirm it?

Amy Yuen: If it's a situation like this where I say, oh, there is a strong candidate. When I look at this family, there is a really strong candidate on my list. I will check that out first. If I look at them and I see the number of possibilities is so wide, or I cannot identify a good candidate, then exome is a good first step.

- Mika Sinanan: And how often is the next step saying, well if it can happen in one area, it could happen anywhere. So, we ought to check the entire genome?
- Amy Yuen: I'm not sure what you mean.
- Mika Sinanan: Well, I could imagine something else with a defect, like an airplane that has missing some screws. If it's missing screws in one wing, you worry about the other wing. Right? So, you check the other wing. How often do they expand beyond the single to focus testing from an ordering standpoint?
- Amy Yuen: Um . . .
- Mika Sinanan: To do a whole exome sequencing.
- Amy Yuen: . . . it would depend on how that first test came back.
- Mika Sinanan: If it was positive . . .
- Amy Yuen: If it's positive . . .
- Mika Sinanan: . . . then you wouldn't do it.
- Amy Yuen: . . . I stop.
- Mika Sinanan: It would only be if it's negative. OK.
- Amy Yuen: If it comes back positive, I look at the case. I see this, this is clearly a match. I am confident this fits. And then we stop.
- Mika Sinanan: And if the patient doesn't respond to the medical therapy that would otherwise indicate that it would . . . that they should, is that a reason to go back to genetic testing?
- Amy Yuen: Potentially, because at that point, I might say, oh, I thought I had a match, but now I have more information. This is not a match. I need to go back to testing. And that's a case where you would then say, OK. I'm back to the proverbial drawing board. What do I do next? Maybe it's the WES.
- Nedra Whitehead: There was another question? No. Alright.
- I know the second one has . . . this is one of the conditions that maybe worth doing WES in an adult. Some of the others, some of the adult onset,

particularly neuromuscular disorders that are caused by a lot of different genes that all present with very similar phenotypes. It comes down to whether WES or trying to do a panel is cheaper.

WES is not regulated by the FDA as a diagnostic test. The FDA does regular sequencing platforms if they're specifically marketed for clinical testing. If someone is selling a kit or a process for clinical sequencing, those would have to require FDA approval. If it's a laboratory that's using its own sequencing platform, those do not. Laboratories conducting WES have to be accredited by CMS. And then Clinical Laboratory Improvement Act to conduct high complexity testing.

Gregory Brown: I'm sorry. I just want to make sure I heard correctly. So, if it is an in-house sequencing, they don't need FDA approval.

Nedra Whitehead: That is true.

Gregory Brown: Even though they are . . .

Nedra Whitehead: The FDA does not, that's called a laboratory developed test. And the FDA does not regulate any laboratory developed test at this point. They've proposed it at least twice that I know of, and I have never seen it get past the public comment station.

Gregory Brown: . . . OK.

Nedra Whitehead: I'm going to skip this slide. It's already been discussed in better detail that I have.

We'll talk about the methods for the review. So, this is the analytic framework that reflects the key questions that were presented earlier with the study selection criteria. So, we included studies of people of any age who were suspected to have a genetic condition and who had been at least clinically evaluated. We included studies that compared tests and pathways that included WES either alone, in comparison with other genetic testing, to no genetic testing, or testing pathways that included WES but compared different times of doing WES. We also included the outcomes of interest, clinical utility, health outcomes, safety outcomes, and cost. Diagnostic yield was included as a contextual question, which means we did not do a [inaudible] assessment on those studies or grade the overall body of evidence. We did systematically go through to identify all [inaudible]. We included a wide variety of study arms, basically anything other than case reports that had less than five people. [inaudible] really wasn't being used clinically.

This was a tough topic to use standard evidence based medicine methods for and systematic review for. The risk of bias, using risk of bias instruments are not really designed for observational studies. They're especially not designed for single arm observational studies that are designed to measure one parameter comparing your cost different interventions or different groups.

Female: We're having trouble hearing on this side. Can we [inaudible] your microphone?

Nedra Whitehead: OK. That's better? Sorry about that. They're often not designed for diagnostic tests. Even those that are, or not designed for genetic tests. So, after considering all the existing instruments, we actually developed a risk of bias instrument for this review to use with the efficacy and the safety studies that address the major domains that are addressed in risk of bias, selection bias, misclassification, and other issues. We did use an existing instrument called the quality of health economic studies for cost outcomes, but that risk of bias assessment is predominantly for cost-effectiveness studies and most of these were just studies of cost.

[inaudible] independently assessed the risk of bias for all included studies, except for the qualitative studies. We did not do risk of bias assessment on qualitative studies.

GRADE. I never do standard intervention reviews. GRADE is an approach that is used to evaluate the quality of the evidence. It's designed around randomized controlled trials of medical interventions, and because of that, they really only start consideration of randomized control trials as high evidence. It never works well for any of the reviews I do. It didn't work well for this one either. So, observational studies start at low, because of the limitations with the study design. Again, these are considerations that are mostly around comparing one thing to another, as opposed to trying to measure a particular parameter in a study.

The risk for using GRADE for this is that as shown earlier, it's really very hard to get a rating above low. With the study designs that are used for this, and it may, in some cases, underrepresent the strength of the evidence for studies that when it's because it's designed to measure an outcome . . . or the studies that are designed to measure outcomes rather than to compare outcomes between two different testing strategies.

So, we screen 5567 titles and abstracts with 431 full text articles. In the end, we included 60 articles and 57 studies, of which 30 addressed the

efficacy outcomes, 26 addressed safety outcomes, 17 addressed cost outcomes, and our evaluation of the contextual question on diagnostic yield was based on 103 studies. I will draw your attention to the study design abbreviations at the bottom here. So, CCS is a controlled cohort study. CQ is a cost study. CS is a case series. EQ is an efficacy question. MS is modeling study. QS is a qualitative study. RCT is a randomized control trial. SQ is a safety question. SR is a systematic review. UCS is an uncontrolled cohort study. Those are used throughout the evidence slide.

So, we have four systematic reviews of the presented data on the diagnostic yield of WES. Two of them actually gave the average diagnostic yield across their studies instead of just a range. Those two had an average of 39 to 42%. Of the 99 individual studies we looked at, and we did a mean diagnostic yield was 38%. A diagnostic yield of WES was higher than any of the other genetic tests they looked at. So, CMA runs somewhere between 8 and 10%. Whole genome sequencing is a little higher. I think that's based on one study. Panel testing runs between 20 and 30% depending on the particular panel and the condition. Just overall, just is a traditional pathway used in this research center runs just over 20%.

This is a question that came up earlier about the diagnostic yield of WES by age. For infants, it's over 40%. For children, it's about 37%. In adults, it sits right at 20%. So, even among adults, diagnostic yield is higher than most other genetic diagnostic tests with the exception of gene panels whenever you can identify a good gene panel.

John Bramhall: Nedra, can I just ask, a diagnostic yield here means there's a variant that is identified . . .

Nedra Whitehead: It means you've found an actual variant that was considered either likely or known to be pathogenic for the condition that the patient present.

John Bramhall: So, it's not, it's not just any variation that's found?

Nedra Whitehead: No.

John Bramhall: OK. Alright. So, it's when it's associated with the disease at hand?

Nedra Whitehead: Right. If you did whole exome sequence on anybody in this room . . .

John Bramhall: Yeah.

Nedra Whitehead: You would find someplace around 20,000 variants.

John Bramhall: Right.

Nedra Whitehead: Hopefully, for all of our sakes, some of them would not be pathogenic, at least in the number of copies you're carrying, but yeah. So, it is specifically this variant, there's good evidence that it causes disease, and it causes the disease the patient has. The symptoms the patient has. That's what it requires to be for that to count as a diagnosis and diagnostic yield. Then, the number of patients with a diagnosis compared to all the patients that were tested in the study.

We looked at any phenotype for which we had at least three separate papers that looked at the same phenotype and found a range between about 28% diagnostic yield for patients with neurodevelopmental disorders to 48% specifically for limb-girdle muscular dystrophy. This is one of the neuromuscular disorders I mentioned earlier. There are at least 40 genes that cause a presentation that looks like limb-girdle muscular dystrophy, and it onsets anytime between childhood and early adulthood.

Gregory Brown: I'm jumping ahead a little bit in your report, but I find this misleading, because the top of your list is epilepsy at 40% diagnostic yield, but then later you say that it doesn't effect seizure control, like 3% . . .

Nedra Whitehead: In the studies that reported on seizure control.

Gregory Brown: . . . right. OK.

Nedra Whitehead: Of which, it's relatively few studies that they, any . . . the larger . . . there's a larger number of where they changed the medication. There's relatively, like, 3%, I believe is the number of patients where they changed the medication, and they got better seizure control. So, it's not that . . . in some cases, there may not be a treatment yet on the market that addresses that disorder. In some cases, they may not, at the time they published the paper, had yet found the right medication for the seizure control and that.

Gregory Brown: That's where I'm getting at is, it calls into question this concept of well, if we order a test and it changes our management, then that's . . . it says the test is worth getting. Well, we changed our management, but only 3% of the population had any better control. We're rearranging the decks on the Titanic, but it didn't change the outcome. So, that's . . . I guess that's what I'm getting at.

Nedra Whitehead: Yeah. So, several things go into that. One is, what actually do you find in the diagnosis. So, in those cases where it changed the management, they

thought they had one form of genetic epilepsy, and it turned out that there was another, that in fact, they had a different form, and there were, there were medications that addressed each form. So, they changed the medication and got better control, but in a condition that has a lot of different genetic causes to present the same phenotype. That is just of the biology going to be a relatively small proportion, but you have no way of knowing when you look at the patient ahead of time whether or not they are going to be somebody who benefits immediately from that or not.

Gregory Brown: OK.

Amy Yuen: Can I add one other comment? Sometimes, even if it doesn't change the medication, or the specific treatment, it might change other studies that they don't need to keep getting anymore. So, particularly with the example of seizures, if a diagnosis has not been found, and the child has severe seizures, the neurologist may need to continue to do periodic MRIs, and if this is a child, this is probably with sedation. So, they need to do a costly sedated procedure to see, has anything changed on the MRI, but if they can find the diagnosis and they can understand, well what is the trajectory? What is expected with this? Maybe I don't need to keep doing these MRIs every year or every other year that can take a burden off of that child having to be sedated and have an MRI. That can also save a lot of money.

Nedra Whitehead: Sometimes, things aren't reported, and sometimes there are things that are reported, but not easily quantified. So, there is at least one of these papers talking about epilepsy where they took them off of a drug that had . . . was known to have severe side effects longterm, because it was not going to address her condition, once they knew what the actual genetic cause of that was. They didn't have another drug to put them, but they did offset a drug that was expected to have longterm side effects, but they didn't follow them long enough to measure that. So, it doesn't show up in the evidence.

I will agree with you, having done this clinically for a while, and I'm sure Dr. Yuen would . . . it's a really frustrating field.

This is the reanalysis and the effect on diagnostic yield. So, if you go back and you reanalyze exome data that you've collected previously, general timeframe is six months to a year, 17% of patients across eight studies who had not received a diagnosis on their first analysis were diagnosed on the second analysis. Now, this is a combination of the effect of better variant calling bioinformatics over time and more genetic knowledge over time.

John Bramhall: Those are data reassessments. This isn't a whole WES repeat. This is just reevaluating the data.

Nedra Whitehead: Reevaluating the sequence data that you've already got.

John Bramhall: Got it.

Nedra Whitehead: In one study that had looked at how many of their previous diagnosis had been retracted based on the reanalysis, only patients with developmental disabilities, 12% of them that had a variant that they had originally thought caused the condition, on more knowledge, they felt did not. The other thing that's happened over time is, people have gotten much stricter about what it takes to say that a variant causes a condition. If they had used their current interpretation guidelines, it would have only been 7%. This probably, to some extent, the other cause for the data showing that originally they were only doing individual WES. Now, almost everybody does trio is what we found out, but we don't know when we thought we did.

If you look at the WES reanalysis versus doing whole genome sequencing in an undiagnosed patient, about 6% of patients were diagnosed by whole genome sequencing that were not diagnosed by WES reanalysis. This is one study only, but it is a head-to-head comparison of the same patients.

We looked at analytic validity. This is originally in harms, but the way we wrote our study criteria required that the inclusion studies be patient, people with a genetic disorder, the analytic validity studies were actually normal people, and they were just looking at whether or not they got different variants in different runs or using different sequencing platforms, or compared to Sanger sequencing, which is the gold standard for sequencing. Of all single nucleotide variants, multiple runs, same samples, 2 to 5% depending on the platform, gave different answers across different runs. Or rare variants, it was higher. It was 4 to 6%. The discordance between WES and Sanger sequencing was 3%. These are both based on one study.

Any questions on diagnostic yield, reanalysis, or analytic validity before I go into the effectiveness questions?

OK. So, each of these have three slides. There's the summary of the studies. There's the summary of the participants. Then, there's the evidence summary. Sorry. Excuse me for a second. My computer decided to lock up. So, 30 studies provided evidence on the clinical utility of these tests. Of these, one was a controlled cohort study, and the others were

uncontrolled study designs. Over half the studies were conducted in the U.S. Of the 22 studies that reported a funding source, just under half were at least partially funded by industry, which includes laboratories that do genetic testing. Half of the studies were rated as having some risk of bias, and the remainder of the qualitative studies were rated as having a high risk of bias. We had one study that reported in an article that was basically a qualitative study design nested in a bigger study that on the diagnostic yield, we did not do risk of bias.

Overall, gender was balanced, though in some studies there were more males and some there were more females. Most studies were of children, either mixed age groups, and most included diverse phenotypes. Equal numbers either tested no family members or only tested patients. Both of those were about 10 and counted for two-thirds of the studies.

12 to 10% of studies that reported patients had any change in clinical management, 5 to 25% had a change in medication based on the WES results. So, this is looking at those patients who had a diagnosis, and of those, how many had a change either in clinical management or in medication and genetic testing for family members changed between 4 and 97% of the time. Amongst that, patients with epilepsy 0 to 31% had a change in clinical management, and 0 to 20% had a change in medication. Other phenotypes all reported some change in clinical management, but the data was just too heterogenous for synthesis.

Health outcomes, we only had seven studies. Of those, one was a controlled cohort study, and the others were single arm study designs of one kind or the other. Again, they were sort of most, about half, were U.S. studies. About half had some industry funding. There were none that were low risk of bias, 2 that were some, and 5 that were high risk of bias.

Again, gender was pretty balanced. Most studies were of infants and children. Approximately half the studies included diverse phenotypes and half only included participants with epilepsy. Half only did single and redid WES test.

The evidence here was too low to even be able to assess what it was. It was very heterogeneous. We looked at mortality and then seizure control or behavioral management in the studies of epilepsy. Mortality was not usually compared. It was 17 to 57%. All those studies were conducted among infants in NICUs or hospitalized children with an acute illness. Those kids would be at risk of high mortality.

- Mika Sinanan: So, question. Over that time period, in some of those studies you pointed out, start in 2012. Right? Did the reference genome change? Or was it . . .
- Nedra Whitehead: The reference genome has changed every, at least every few years, as we know more about the genome and the variants. It's updated.
- Mika Sinanan: So, are the . . . and the number of pathological abnormalities is increasing over time, too, to be identified.
- Nedra Whitehead: The number of variants that you know are nowhere pathologic compared to the ones that you don't know has changed over time. Yes.
- Mika Sinanan: So, that . . . it's really a moving target. Those numbers are . . . it's one of the reasons for the very wide confidence intervals.
- Nedra Whitehead: It's a moving target, in part because of what we know or don't know about variants and whether or not they're pathogenic, and in part because in the whole population of people with genetic disorders, it's huge and varied, and the actual participants in any one study are relatively small. So, a lot of it depends on what the people that you actually have had as a genetic, which genetic disorder they had, because some genetic disorders are much more amenable to treatment than others, because you know more about them, because it happened to be that there was a pharmaceutical that, you know, has a major impact on the protein defect for a variety of reasons. There's just, some have much . . . there's just much more you can do about some genetic variants than others.
- Mika Sinanan: So, I have a sense then that studies that use a more contemporaneous or closer to now comparison have a higher yield?
- Nedra Whitehead: Yield is definitely going up. Part of that is a reference variants. Part of it is what you know about the variants. Any clinical study will use the reference variant that was the latest at the time that they did their actual test. At least most of the ones I have seen will put that reference variant, the genome reference variant, not the individual gene reference variant sequence in their report. Or else, you can call and get it, but it's just a field in which basically we know the tip of the iceberg about all conditions that are in the population. So, as the knowledge gets greater, our ability to diagnose gets greater and our ability to treat gets greater, because new treatments come on the market.
- Mika Sinanan: OK.

John Bramhall: Do you mind just going back to the previous slide if you can? Just so I understand it. So, here what this slide . . . you've got it labeled health outcomes from testing. Am I understanding it correctly? There are four studies that dealt with mortality. And in those studies, whole exome analysis was conducted, and the patients died at a certain percentage.

Nedra Whitehead: Yes.

John Bramhall: Even though they're applying [crosstalk].

Nedra Whitehead: There are four studies that reported mortality. None of those studies were designed, per se, to look at the effect of whole exome sequencing on [crosstalk].

John Bramhall: Right. But these were seriously ill children who died?

Nedra Whitehead: Yes.

John Bramhall: And in the improved seizure control, maybe you don't know this from the studies, it's possible here that the WES elucidated, identified a cause for the seizures, but it doesn't make any difference, because you're going to treat the seizures symptomatically. Is that the right interpretation? I mean . . .

Nedra Whitehead: Well, so . . .

John Bramhall: . . . oh.

Nedra Whitehead: . . . there were, the studies looked and diagnosed kids with WES. In some cases there were treatments that were aimed specifically at the pathway that those kids were diagnosed with. So, the kids weren't . . . those are not cases where kids are being treated symptomatically to reduce seizures. They are being treated with a pharmaceutical that is better to address that pathway.

John Bramhall: I see. That's different. So, two studies, WES was conducted. A lesion was identified. A treatment was initiated that was pertaining to that lesion, and it . . .

Nedra Whitehead: In a certain percentage of the patients.

John Bramhall: . . . I get it. That's helpful. Thank you.

Nedra Whitehead: Yeah.

- Seth Schwartz: I had a question. I'm still struggling a little bit to think about mortality. So, in terms of how WES was used, so what I'm trying to understand is, what does mortality mean? In other words, were you trying to identify a cause that might have predicted a nonviable phenotype, in which case you might have withdrawn care? In which case you would have expected mortality to have been higher in those patients? Is that the scenario? Or is it that they identified an underlying cause that could have been treated to improve survival? I guess, I'm just not sure exactly how WES is used in this scenario of these critically ill children.
- Nedra Whitehead: Basically, the article was being . . . the purpose of the article was to report on a diagnostic . . . it was much more designed to report on the diagnostic yield of using WES in that particular population. And they . . . we extracted mortality, because they did report it, but they . . . it was not designed to evaluate the effect of WES on mortality or to sort of systematically look at that. So, there's no breakdown of . . . so how many of these, you know kids turned out to have a condition that was lethal.
- Seth Schwartz: But just understanding the clinical utility, Dr. Yuen, could I maybe ask you that question? So, how is WES used in this . . . particularly in like the NICU situation where you have a critically ill child?
- Amy Yuen: It would be helpful in finding, do we have a condition that has a specific treatment? Or do we have a condition where we know the prognosis is very grim, and we can let the family have that information early, so they can decide what type of interventions they want for their baby. So, this summer, I had a baby who started having seizures in the delivery room. He went to the NICU. The neurologist saw him. The EEG was very abnormal. This is a severe seizure disorder. So, we were able to get one of the rapid exomes done and found out very quickly the genetic cause, did not have a specific treatment, and babies with this die in infancy. So, we could provide this information to the family early. They were able to connect with the palliative care team. They could decide, do we want a G-tube or not. Do we want to do a trach or not, and it shortened their NICU stay, because we knew they could make their choices on their interventions, and they got to leave and enjoy the time they did have with their baby. Another child that we had around the same time ended up having an atypical form of pyridoxine dependent epilepsy, which in the past, they had thought you could find all these patients by infusing pyridoxine and seeing if they responded, but as we've done more panels and WES, we've found there's actually a wider range, and there are some children who don't respond immediately on an infusion of pyridoxine. You need to know they have the diagnosis, start the treatment, and continue the treatment.

Then, they improve. So, that was a child who appeared to have an intractable epilepsy, and they had started multiple medications that were able to be weaned off. Now, she's just treated with pyridoxine. So, we see a wide range of how this impacts the care.

Seth Schwartz: Thank you.

Mika Sinanan: Well, what is the time interval for a rapid WES?

Amy Yuen: You can get them in about seven to ten days. So, that was very helpful in the NICU situation where we think of the NICU as . . . that it's stressful on the family. It's very expensive. We're using a lot of healthcare resources. So, if we can figure out how best to take care of that baby quickly, if we save a few weeks in the NICU, that is good for the family and good for the healthcare system.

Nedra Whitehead: For safety outcomes, we looked at misdiagnosis. We looked at secondary findings, and we looked at psychosocial harms. And as was mentioned earlier, secondary findings can . . . you can either think of it as a harm because of its unexpectedness of the information, or as a potential benefit, because it's the information you may not have found that you can actually do something to possibly effect your health.

We had one study that addressed misdiagnosis. The study was rated as having some risk of bias, and it did not have any industry funding. The participants were children with neurological disorders. There's 2% of the patients that were diagnosed with standard testing were not diagnosed by WES. Undiagnosed patients had genetic variants that were not diagnosed well by WES at the time of the study, i.e. things like copy non variants and uni-parental disomy, also heterogeneity.

22 studies provided evidence on the prevalence of secondary findings, 15 were conducted in the U.S., and 14 had no industry funding, 11 studies were rated as low risk of bias, 9 as having as having some or high risk of bias. There were two that were qualitative study designs that reported findings from background studies.

Gender was balanced. Most studies were of children. Most included diverse phenotypes, 13 studies included testing for family members, either parents or other relatives.

Among the 13 studies with data suitable for doing a pooled analysis, 4% of patients had an ACMG-medically actionable secondary variant in the studies that reported, 90% of the patients had chosen to receive that

information on secondary findings. We rated the strength of evidence on this question as low.

Eight studies, all conducted in the U.S., provided evidence of psychosocial harms related to WES testing, 5 were qualitative studies, and 3 were uncontrolled cohort studies, 1 study industry funded. Of the three quantitative studies, two had a low risk of bias. One had a high risk of bias, and as I said earlier, we did not assess risk of bias for qualitative [inaudible].

On average, more participants in these studies were women. A good deal of that is because a lot of them were caregivers of pediatric patients. Of the studies reporting age, most included only adults. All studies included participants with diverse phenotypes. Only one of these had trio testing.

Most patients or parents of patients did not experience psychosocial harms either from receiving negative or uncertain WES results. There were relatively few mentioned in report effect on family relationships, and we were unable to assess the strength of evidence because most of these were qualitative studies, which don't fit well in the risk of bias or the GRADE.

Mika Sinanan: How long is the followup on these? Sorry.

Nedra Whitehead: It varies. Often, it's a study that went back or recruited from a longitudinal study of WES on pediatric patients so that it's done like once at some point after they receive the WES.

Mika Sinanan: One assessment.

Nedra Whitehead: One assessment of psychosocial harms after they received the WES results. In some cases, patients were . . . in at least one study, patients were in . . . or parents of patients both before and after they received the WES test.

17 studies provided evidence on the cost or comparative cost of WES, 8 of these studies were conducted in Australia, 8 had some industry funding, 11 had some risk of bias, and 6 had a high risk of bias. Most were studies of children, 3 included individuals of any age, 10 included diverse phenotypes, and 7 were single phenotype populations, 9 did trio testing, and 8 singleton testing.

And the cost of WES ranged from \$1000 to \$15,000 U.S. dollars. The health cost per diagnosis for WES compared to standard testing ranged from no additional cost to over \$8000. Trio WES generally cost more than singleton WES. Earlier, WES testing was more likely to be cost-effective than

conducting WES later in the testing pathway, but overall, the strength of the evidence here is rated as very low.

There are no clinical practice guidelines that we could find for WES testing. Two professional societies, the American College of Medical Genetics and the American Association of Neurology have issued recommendations for when to order WES. Both societies recommend WES for cases that are undiagnosed after specific genetic testing that have nonspecific or clinically heterogeneous phenotypes.

There were four previous Health Technology assessments for WES, but we were unable to review those, because two were non English language, and two were publically accessible.

So, in summary, WES changes management for between 12 to 100% of diagnosed cases. WES-guided management changed health outcomes in 1 to 3% of patients with epilepsy. Approximately 4% of patients with WES will have ACMG-medically actionable secondary finding. WES costs between \$1000 and \$15,000 U.S. dollars. The difference between costs to [inaudible] traditional testing very considerably. The pathways that include WES were more likely to [inaudible] WES earlier in the testing pathway were more likely to be [inaudible].

The evidence base had substantial limitations. There were no randomized trials comparing WES to non WES-testing pathways, and there were very few studies of clinical utility or health outcome. Very few studies used standard protocols for outcome data collection, and only if you included a comparison group.

This was discussed earlier in more detail, but CMS has no national coverage determination for WES. This is something I meant to mention earlier. We limited our review to [inaudible] or actually people's total genetic makeup. The CMS coverage policy regarding cancer is for tumor testing where the genetic makeup changes, as the tumor progresses. So, they're not really comparable policies. They're used differently. They have different interpretation. Some clinical payers cover WES for beneficiaries who meet the specific criteria.

We found 15 ongoing studies relevant to this review. One study being conducted at the University of North Carolina addresses many of the limitations in the evidence base. The study is a randomized clinical trial with four study arms evaluating WES. Pre-visit preparation for WES, parent patients in the pre-visit prep arm we see education materials and a question prompt list that they can use at their scheduled visit. All the

others are single arm observational studies, apparently similar to those that were included in the review.

The limitations of our assessment was that we only included English language articles, and studies focused on diagnostic yield did not undergo risk of bias assessment, and that body of evidence was not subject to a GRADE assessment. We limited our search to three databases, but we also searched the bibliographies of the included papers to see if there were any articles of reference that we missed.

In conclusion, this is actually a typo for the moderate. That is low, not moderate. I misread my color. I typed it in the slide and put the wrong shade of yellow. Any questions?

Gregory Brown: I think we're gonna take our break. I've got 10:25. So, how about 10:40 we'll come back for questions and then our discussion. OK? See you in 15 minutes.

If we could reconvene. Kevin?

Kevin Walsh: There had been some requests for including the price of the counseling before and after to understand what the real cost of this technology was, since it didn't happen in isolation. That was a great request. Thank you, Janna. I'm wondering if we have that available?

Gregory Brown: I don't know. Were we able to find that?

Josh Morse: Dr. Johnson, could you . . .

Dr. Johnson: [inaudible]

Gregory Brown: OK. If you could do that, that'd be great. So, we're reconvening. We have finished our report. Now, it's time for questions of our contractor. I, and a number of us, are not very bashful. So, we got a lot of our questions answered on the way, as we go, which hopefully is in better context than trying to do it all the end. So, anyway, we're open for questions from the committee, either contractor or clinical expert.

Tony Yen: I have a question for our clinical expert. For the clinical utility part of WES, would it be fair to say that it's more, like, 4%, because it's approximately 4% of the ACMG-, I'm sorry. I can't remember the exact acronyms of the society of the medical genetic society, in terms of those very specific diagnoses. I'm just trying to really understand the clinical utility of WES?

- Amy Yuen: You mean for the primary diagnosis or for the secondary?
- Tony Yen: For the primary.
- Amy Yuen: Well, it depends on how you look at utility. When you find the diagnosis, you may have instances where there is treatment or stopping of other testing, or moving to palliative care. so, I have found if you look at it from the broad approach, the utility is quite high. In almost every situation where we have a diagnosis, there is some degree of utility either in the treatment, not doing another test, palliative care, or relief to the family, and finding the diagnosis and being able to stop seeking additional consults and opinions.
- Tony Yen: Would you say that's higher than 4%, in terms of, like, what [inaudible]?
- Amy Yuen: I would say it's much higher.
- Nedra Whitehead: Just mathematically, if it's almost all of the cases that have a diagnosis, and on average you have a diagnosis in 40% of cases, then it would be 40%. The 4% has nothing . . . I secondary variants. It has nothing to do with the primary diagnosis.
- Tony Yen: I apologize. I'm looking at your slide over here, about 4% of patients tested with WES have ACMG medically actionable variant.
- Nedra Whitehead: That's a secondary.
- Tony Yen: So, that's secondary diagnosis?
- Nedra Whitehead: That's secondary findings that, I mean, theoretically if we tested everybody in this room, some of them might very well have a secondary medically actionable variant depending on how that's diagnosed.
- Tony Yen: So, you didn't . . .
- Nedra Whitehead: Not the primary indication.
- Tony Yen: . . . OK. So, you didn't assess some sort of percentage for the primary diagnosis?
- Nedra Whitehead: That's the 12 to 100% that was reported in the clinical utility.
- Tony Yen: OK.

- Nedra Whitehead: And that was the best evidence we had.
- Sheila Rege: Question on page in the report is 30, and this was on health outcomes, and it says mortality. I know we've talked about this, but we say range 17 to 57%, that's not implying that the lack of WES testing caused mortality/
- Nedra Whitehead: No.
- Sheila Rege: That is just . . .
- Nedra Whitehead: That is the mortality among those patients that had WES, and it doesn't . . . the studies did not have a comparison. It was just a report of mortality in those populations.
- Gregory Brown: So, just to . . . so my understanding is, there's a group of NICU patients. We got WES to see if it helped us treat, and in that population, there was this mortality rate, but there is no relationship to the WES testing and the mortality rate.
- Nedra Whitehead: That is correct.
- Gregory Brown: OK. It's simply in that group of population of patients.
- Mika Sinanan: So, if we . . . imagine that WES was not available for administrative reasons, not paid for, not a covered benefit, what would genetic counselors and families do? Or what would you recommend in that situation?
- Amy Yuen: If it's available in the world to order but not covered by their provider, we've had instances where that has happened where we thought a WES would be helpful, and we asked their insurance provider, and coverage was declined. We've had some families who then said, well what is the cost to me if I go pay for this. So, we've had some families who will then pay out of pocket. We've also had other situations where we thought it was very helpful. Insurance declined to authorize it, and the family did not have financial means, and we've used money from our charitable foundation to pay for exomes for some families.
- Mika Sinanan: Are you aware of patients who would . . . you thought, would clearly have benefited from it, but because of the coverage decision, did not get it?
- Amy Yuen: Yes. We've had a good number who we thought would benefit, but we were not able to find a financial avenue to cover it.
- Mika Sinanan: And what do you do then?

- Amy Yuen: You see them back in a year or two years, and you keep trying, either through clinical evaluation to find something that becomes apparent over time. Or you ask the insurance again in a year or two and see if they have the same answer. So, I've had some patients where it was denied on our initial request, and the child comes back the next year. We send a new request, and it's approved, and we proceed.
- Mika Sinanan: But you don't use a panel of either single or array testing to look for . . . to sort of replace the WES?
- Amy Yuen: If we can identify something that might be helpful, then we would try a panel. For many of these patients, before we've gotten to the point of asking for the WES, I've done anything that would have made sense logically to test already.
- John Bramhall: So, are we at a point . . . my assumption is that we're at a point clinically now where panel testing may, in some circumstances, lead to a genetic therapy. Is this . . . that's the case?
- Nedra Whitehead: Yes.
- John Bramhall: Can the same be said for exome testing?
- Nedra Whitehead: Yes.
- John Bramhall: It can? So, absent a panel, WES intervention is run a set of lesions or a single lesion, a single change is identification, and there are instances where that would lead to a genetic intervention, or genetically manipulative intervention, rather than a chemical treatment?
- Amy Yuen: Yes, and I expect the number of those to increase dramatically in the next few years. There are many companies working on new gene therapies that are going through their FDA studies or they're in early development. So, I expect, especially over the next five years, we will see a large number of new gene therapies. These will be very specific to the genetic etiology of that person's symptoms. They will need to know the gene involved to know whether that therapy will help them or not.
- John Bramhall: And I just want to know, when those are identified, which they have been, are those lesions or those changes incorporated into the new panels at that point so that the testing can be done on a more simple fashion?

- Amy Yuen: So, the more we know about these, the more the laboratories can adjust what genes are on their panel, and the better information they'll have in their algorithms when they review the results to be able to identify the pathogenic mutations.
- Sheila Rege: So, I'm still on safety and harm as I'm kind of thinking about it. So, we've talked about the fact that these labs have their own panels. Some are proprietary. Are there certain labs that you would say, oh, I would never send my things there, and is there some way . . . some criteria that are used? Or all labs pretty OK, I mean pretty comparable?
- Amy Yuen: Most labs are very high quality. They have CLIA. We know from our community from hearing, us at Mary Bridge, we'll talk to the people at Seattle and hear if they've had any problems with any labs. We'll talk amongst ourselves. So, we have found there is a large number of very good, high-quality laboratories out there.
- Mika Sinanan: Dr. Fortinos presented a safety concern that was high. I talked about this earlier and asked a question about it. Your safety data . . .
- Nedra Whitehead: We found no evidence for substantial concerns from negative or uncertain results, which there was a reasonable amount of evidence for, and even the one mention in a paper of when the WES results resulted in a finding that the family relationships were not somebody thought they were, that it was sort of an adjustment, but it didn't cause any major problems. Now, I certainly, there were no studies that addressed that across the board. I think anybody who has ever seen families know that some families that would not be the case, but those families may very well choose not to do WES testing anyway. It is not limited to WES testing. It just comes up more often.
- Mika Sinanan: What was the timeframe of followup [crosstalk]?
- Nedra Whitehead: It was a qualitative study. So, it was done after the WES testing. It wasn't a longitudinal study with followup, but it had been done. The study had been done long enough that people sort of had some time to talk about it. So, I had forgotten exactly how long after the WES testing it was done, but it was not the initial genetic counseling immediately following the WES.
- Charissa Fotinos: I just want to make a couple of clarifications. Part of the safety concern on our end was also how well variants of undetermined significance be interpreted if they are presented, learning more about the actual process and way in which they're reported had less of that concern, as we were going through the actual review. I think that was in part what led us to

recommend that we want to have an expert both order it, evaluate, interpret it, and give it to the family. Two followups, Medicaid reimburses \$28 for every 30 minutes of genetic counseling. That does not include all of our insurance, so, Public Employee Benefit. So the rates that they pay may differ, and just a reminder that even though I say Medicaid a lot, this is really meant to be both our Public Employee program and Medicaid, and as of January, all our school employees, as well.

Mika Sinanan: The safety concerns that we just heard correspond with your impression.

Amy Yuen: One of the reasons why we also like to have either a geneticist or a genetic counselor involved in the pretest counseling is to let families know about potential issues, particularly as mentioned, if you test a family trio, and the parents are not who they are thought to be, that will be identified on the testing. That can be very disruptive to a family dynamic. So, they need to know that that is a possibility. I've been incredibly lucky, and that has not come up with any family I have tested so far, but we let everyone know ahead of time. Then, we also let them know about the secondary findings. So, they can choose, do they even want the secondary findings or not. I've found the majority of families choose to accept the secondary findings. Some will say no, and even if they say, no, I want to know everything, we have them pause. Then, I will list for them what are the pros and cons. So, even if they are set, I want to know everything, I'll say, OK. So, these are the reasons why people might want the information, and here are reasons why people might not want the information. So, I will tell them. Some people, indeed, want to know everything. Some people do not want this additional information. They're already dealing with one medical challenge, and it could be overwhelming to find something else that you weren't expecting. It could potentially impact life insurance, not just for that patient, but for the family members being tested. If we find some secondary finding they weren't expecting that could impact their longevity, and they go to apply for life insurance where their medical information is required. So, it wouldn't impact if they get life insurance through their employer, if their employer is giving it to them as a standard benefit with no medical review. It won't hurt that, but if they want to apply for an additional life insurance policy, and they need to provide their medical information, that information could impact them. So, we have had actually some families say, hang on. We're gonna go check our life insurance policies, decide are we set with what we want. So, don't check the box yet for secondary findings. We'll call you back tomorrow or in a week and tell you whether we want to proceed or not. So, I think getting that information and knowing kind of eases potential harms, or reduces the risk of potential harms.

- Sheila Rege: And this may be getting ahead, and for both of you and maybe the medical director, too. I don't recall if it was in the scope of what we asked for, but I remember some discussion at onset earlier in the year about fetus testing with the WES, is that excluded in this scope?
- Nedra Whitehead: Excluded from the scope.
- Sheila Rege: OK. Thank you.
- Mika Sinanan: For our expert, the value of this, in terms of the number of defined abnormalities is increasing, the cost has come down over time. To the extent that you're aware, do you have any idea what the cost is going to settle out at? I mean, is it, has it been flat? Is there a floor to this? Or is it going to come down to a marginal cost of \$20?
- Amy Yuen: I don't think we'll hit that low, but we could see a trio exome settling probably somewhere between \$1000 and \$2500.
- Mika Sinanan: For all three or individual?
- Amy Yuen: For all three. Right now, there are laboratories that will do a trio for \$2500.
- Gregory Brown: 23 and Me.
- Amy Yuen: We do not advise . . . [laughing]
- Gregory Brown: The point is that . . .
- Amy Yuen: I know this is publically recorded comments. So, I don't want to offend anyone in this industry, but . . .
- Gregory Brown: . . . but theoretically, that's your lower cost.
- Mika Sinanan: I don't know how much that costs. How much is it?
- Gregory Brown: I thought it was \$200 to \$500, depending on how much you want. The point is, is that for large scale commercial testing, they can get down to that. I mean, that doesn't have the same sophistication of algorithms, obviously, but I'm just saying, in terms of . . . if it became a standard of care, and it's, like, your checkup is just now, well we want to know the genetics on you when you come into the office. That's kind of . . . so pretty much everybody is getting it. Then, that's . . . again, I'm not proposing or . . . I'm just saying, that's the kind of rates that they're doing.

- Janna Friedly: It seems like in our discussion about potential harms and the counseling that's so important, that is critically important to minimizing the risks and the harms of this testing. Are there guidelines or specific training or algorithms for counselors to follow for this particular testing that is soft of widely used? Or is it very variable what information families are getting from the genetic counselors, especially at places outside of your institution?
- Amy Yuen: There is not a specific guideline of everything to include, but I think most genetic counseling schools would teach their students to include a certain checklist of items, one being explaining well, what is this test? How does it work? Why are we doing this test? How long will it take? What are the possible results? This is very important . . . letting people know their test could be positive, negative, or there could be an uncertain finding. I find when there is an uncertain finding, if patients aren't aware ahead of time that there could be an uncertain finding, they are more confused by that and more likely, from my impression, to appear distressed and concerned that perhaps that is something bad that was found. They need to know ahead of time of the possibilities. Going through the secondary findings and letting them choose, do they want that or not, having the warning about misidentified paternity being detected. Just knowing what to expect from the test. So, I would say most genetic counseling schools would teach that standardly.
- Gregory Brown: So, obviously, Mary Bridge has it, Seattle Children's has it. Other facilities that provide have medical geneticists and/or medical or genetic counseling.
- Amy Yuen: Yes. Well, Kaiser and in Spokane, I think that is the Providence system, they have a geneticist. Both of those institutions have a geneticist and genetic counselor. And when we speak of Seattle, it's Seattle Children's and University of Washington. So, they've got the adults and the kids covered. At Mary Bridge, even though we are a children's hospital, we don't have an age cutoff. So, we will see people of all ages.
- Sheila Rege: Our small town actually, at one time, had multiple and currently has one dominant genetic counselor, which is interesting with the smaller hospitals also having that available.
- Amy Yuen: Many of the hospitals, even if they cannot recruit a medical geneticist have hired one or more genetic counselors. So, even if you're not in one of those cities with a medical geneticist, you may still have access to a genetic counselor.

- Sheila Rege: These are not physicians. So, what is the training? I mean, you're saying genetic counselors. Is that different than a geneticist than a . . . I'm having trouble with . . .
- Amy Yuen: So, a medical geneticist has gone through medical school and has typically then either trained in pediatrics or internal medicine or one of the other general specialties, and then does an additional three years in genetics training. A genetic counselor is a masters program. So, after they have finished college, they go into a two-year intensive masters program that focuses on genetic counseling. That includes clinical rotation. So, it is not just a theoretical book learning. They do their classroom work, and they go into clinical rotation. So, they have a very robust training.
- Mika Sinanan: Within this scope, if you look at page 14 and 15, the medical director recommendations, would they restrict your ability, as you currently practice it, to appropriately recommend or request that WES testing?
- Amy Yuen: I think my biggest concern is with slide, I think this is on . . . the top slide on 15.
- Sheila Rege: Can we project that by any chance? Thank you.
- Mika Sinanan: 14 and 15 are the pages.
- Gregory Brown: I think we're talking about the medical director's slides.
- Kevin Walsh: Slides 27, 28, 29.
- Gregory Brown: So, just to save our vendor from standing here while we discuss, do we have any more specific questions for her? Or, I think we've rapidly . . . so we appreciate it. Thank you. We'll let you sit down and join the conversation from your seat. OK. Well, while we're pulling that up, I mean, I think we're . . . we've got most of our questions, I think . . . it sounds to me like we're starting to get into the discussion phase. So, does anybody want to articulate what they're thinking right now and kind of where?
- Mika Sinanan: At the retreat, we talked about doing the first set of preliminary review assessments and then talking about why we raised our things in a certain way, as part of the discussion. I'm just wondering whether that might not be a good idea to do, but I think it would be very helpful to know whether or not what has been proposed would actually work within what they're currently doing and why not.
- Mika Sinanan: It's slide 27.

- Gregory Brown: It is age 14, not slide 14.
- Sheila Rege: Oh, my fault.
- Gregory Brown: Slides 27 and 28. I haven't given you control. My father was in heating, ventilating, and air conditioning. He did the same thing. He'd put a thermostat in an operating room but not hooked up to anything. So, the staff could put it up or down as much as they wanted, but . . .
- Mika Sinanan: The illusion of control.
- Gregory Brown: . . . it wouldn't mess up the system. That was my introduction to surgery before I became a surgeon.
- Mika Sinanan: We'd check the thermostats in the OR in North Dakota.
- Gregory Brown: Usually when I'm doing a fracture, and I'm wearing lead, I get out and I look like I've just finished a marathon. I stood there for 15 minutes or an hour or whatever. So, again, while we're looking that up, anybody want to . . . actually, I like your idea. Do we want to just go through our three topics. So, in terms of efficacy and kind of see . . . so, we're doing the yellow ones? So, we'll start with efficacy. So, since we're not really comparing to anything indirectly, it's just . . . so is it . . . we'll say the basis standard of care, I guess, whatever that is. So, is WES more effective, equivalently effective, less effective compared to standard of care?
- Josh Morse: I'm going to count more and some's first. One, two, three, four, five, six, seven, I see eight more and some. And if you weren't holding up a more and some, I see two unproven. Thank you. That was for efficacy. Is that where you started?
- Gregory Brown: Yep.
- Josh Morse: OK.
- Gregory Brown: And then in terms of safety.
- Josh Morse: OK. I'm going to count equivalents first. One, two, three, four, five, six, seven equivalent, and three unproven.
- Gregory Brown: Thank you. And there is a cost or cost-effectiveness. If it's more costly, that's one answer. If it's more cost-effective, that's . . . so let's do cost-effectiveness.

- Josh Morse: Again, I'll start with more and some. One, two, three, four more and some, and that would be six unproven. Is that right? One, two, three, four, five, six, OK. Thank you.
- Gregory Brown: Alright. I'm just looking at majorities. We think in some cases it's more effective. We think safety issues are equivalent. I mean, this concept of potential harm and unknown and how do you deal with that? Then, the majority would seem to think that there is unproven, no data, no evidence on cost. As you said, Mika, that was the . . . that's just to see where people are thinking. Since it was your suggestion, why did you think it was more effective in some?
- Mika Sinanan: Well, I think that the efficacy data that we saw showed benefit primarily in children, at least 40% or higher where there was an improvement in the diagnosis. I think that's in the clarity of the diagnosis. I think that that's a moving target, as the number of defined abnormalities is increasing. As the reference genome is refined, and as the accuracy of the lab improves over time. So, since we're making a recommendation that will last for several years, I think it's 40% plus, probably higher in the younger you go, and especially if it is ordered by genetic counselors who recognize the specific phenotypic syndromes or diagnoses that should be tested by more limited and targeted testing, as opposed to WES. So, under those circumstances . . .
- Gregory Brown: I think we'll . . . I'll suggest we . . . you said medical . . . you said genetic counselors. I think you mean medical geneticists.
- Mika Sinanan: . . . OK. Well, either genetic counselors or medical geneticists. The requirement in the recommendation is a consultation. So, it could be either. I would hope that a genetic counselor who is uncertain would refer the patient up to the next level before ordering it, but that was the basis for my opinion about that, recognizing that these are observational studies and that their information is low. I would point out to our vendor that the observational study of jumping out of a high altitude airplane with or without a parachute has fairly high validity. Right?
- John Bramhall: It seems there is, in some cases, benefit in my mind. The benefit is that you're only, at the moment . . . you're only practically going to get to the genetic level because of uncertainty with all the other diagnostic tests that have been applied, or many of them. So, you've got a family population, a population of families, who are unsettled. There is no clear determination of what's going on with their child, for example, in pediatric cases. So, it seems to me, that's a very positive benefit if you can nail something down,

and the data that we were presented with suggests that in a percentage of times, a significant percentage, you can nail it down to the satisfaction of the family. So, I agree with you. I think in many cases, there must be a benefit. The questions that then circulate around in our discussion may be, well, is there a change in therapies. Is there a change in outcome. I think that's a lot harder at the moment to think about, but that doesn't, in my mind, discount the validity and the value of a certainty or a move towards certainty of diagnosis. The other thing, not to stretch it out too far, but we concentrate often on individual outcomes, the individual, yes. So, I think, in some cases, there is an individual benefit, but this seems to be a population issue. This type of approach is a population issue to me. It's not just individuals. It's the generation of information for populations. In as much as the plans, the funds, as much as the Health Care Authority is interested in a population dynamic, it seems to me that if we would support the collection of information that leads to a benefit to the population, that's something that we could pay attention to. The slippery slope is that if you start to generate large masses of information, the push for genetic testing, the push specifically for the exome testing down the cascade of diagnostic routine. In other words, you push it down to being the first thing you do, that has economic and social and scientific implications that are difficult to deal with, but I don't think that's what our decision at the moment is to yield. I don't think so.

Sheila Rege: Just to be a devil's advocate, I was looking at, you know, our grid that we're supposed to use. Efficacy. I remember that slide, 40%, and that's why I said more in some, but then you look at this change in management. That was minimal. Was it 1 to 3% from what I remember.

John Bramhall: Well, for seizures.

Sheila Rege: 12 to 100%. OK. Change in medications, mortality there was . . . and improved seizure control was maybe what I'm remembering at 3%. Yeah, the health outcomes. So, I kind of was vacillating between unproven and more in some. It's totally different, just because of the efficacy. Change in management, change in medication, but no benefit in improved seizure or improved something.

Female: [inaudible]

Sheila Rege: And that was my struggle, in just efficacy. That's all I want to focus on. So, I'm open to others.

Seth Schwartz: I would just have one comment. One of the things we usually do is, we go through them and say, are those really all the appropriate outcomes. So,

I think what we've heard, as we've gone through this discussion is, there are other outcomes that probably aren't captured in that, which is benefit to families, cessation of further testing, other things that we didn't really look at. So, I think there may be some real benefit that is not captured in those outcomes.

Mika Sinanan: I really strongly agree with that point that John has made. I park in the S1 parking lot at the University, which shares parking with the Center for Human Development, and the families with their kids park there. When they take the last slot, and I have to keep driving around, I often am tempted to curse them, but I think, there but for the grace of God, you know? That's why we stopped at two kids, because it's a roll of the dice every time. I think that that uncertainty is a really life-destroying, family-destroying thing. Anything we can do that is reasonable to improve the certainty of their knowledge about their kid and what's going on, maybe if there's nothing that can be done about it, at least it's a target that they can get behind. This is actually one of the reasons that some families have, with huge means or by crowdsourcing, forced the development of novel therapies for rare genetic diseases, which wouldn't have otherwise occurred if they hadn't defined a problem. So, it's a moving target, but it's clearly, as Seth points out, I think, a huge benefit to at least know what it is you're dealing with.

Sheila Rege: And I'm hearing more that we're focusing on children. I mean, I don't know if in the past we've done children versus adults. Do we feel differently about children versus adults on this topic?

Gregory Brown: Two comments. One is on slide 30, not covered for reducing diagnostic uncertainty. That is a specific recommendation from the medical directors, in light of your comments. I actually have to thank Kevin for . . . I think it was you that sent out that three page article on utility for testing. I think with you, [inaudible] also in the . . . we can order a test. We can change prescriptions. We can counsel. We can do everything, but did it change their quality of life. Did it improve mortality or morbidity? The thing that I am struggling with is, there is obviously specific genetic disorders that the only way you're going to find are with WES testing. They have a specific treatment that is unique, because it's a unique genetic variant. For those individuals, it is a dramatic change in outcome, but when you're publishing in the literature, you're not publishing case series of one with a genetic disorder you found. So, trying to find the evidence of how much WES impacts health outcomes is going to be hard to document in the literature. Does anybody, is that what anybody else is struggling with?

Seth Schwartz: It is difficult to sort of contextually understand what we're doing here, but I think we have a test, and we have to look at what the application of it is. I think that what we're seeing is that clearly we have a test that's a cable of detecting where we are now, but there's this continuum of knowledge that's going to increase. So, the utility of this test is going to go up and up and up. It's hard to anticipate exactly what the health outcomes are going to be, that difference, but it's kind of the wave of what's going on in medicine. So, it seems kind of almost inaccurate to look at this in the vacuum of where we are today and not look at the continuum of what's happening. I think when I think about what's my greatest concern about this testing, it really has to do with just wide use of it that's not judicious. I think with judicious use of this test in the right hands, it seems to have applicability that is meaningful to individual patients and individual families. It may actually be cost savings in certain circumstances. If it's widely used, it's probably going to be outrageous, because it's going to be very expensive. It's going to create a lot of situations, a lot of unknowns that may lead to more testing and more expense that doesn't really help anybody. So, I think the agency director's recommendations, while they're very restrictive, make a lot of sense in that there is some applicability of this test, but we want to use it very judiciously with the understanding that the usefulness of it is likely to grow over time. Maybe on re-review when we have significantly more data and more . . . the applicability of this is going to be hugely different when you have 5000 of the 6000 potential genes, as opposed to maybe 1000 of them now. So, I'm just trying to think of it in the context and what the usefulness of this is at the current time.

Janna Friedly: That was exactly what I was going to say. I think that looking at this criteria, reducing diagnostic uncertainty as being not covered for, to me that reflects widespread use in the wrong context without the right counseling and choosing it for the right people to get tested. So, I think my impression is, that's probably trying to get at that . . . reducing that inappropriate use where on slide 28 they say one or more of the following are expected to occur once a diagnosis is reached, medication or other treatments are initiated, discontinued, contraindicated care is discontinued, palliative care is withdrawn. I think that's what came through loud and clear to me was that reducing the diagnostic uncertainty in the right people at the right time can help to ward off unnecessary searching for additional answers and additional tests and additional treatments and consults with specialists that may not be necessary. So, I feel like, to me, if you put in the right criteria here, that becomes unnecessary, this diagnostic uncertainty piece, because I do think that there is value to reducing the diagnostic uncertainty in the right setting.

Charissa Fotinos: That was the intent with which that was written. You said it better.

- Mika Sinanan: We're going to say that you had a limitation or a concern?
- Amy Yuen: I think this is slide 29 when it mentions covered when at least two of the following are present. This could be limiting. Sometimes, we might have a patient who has such severe global delay, but we don't find any congenital anomalies. They don't have seizures, but their delay is so severe, and we've already done the other testing. For example, I think of perhaps a 4-year-old who is still not walking and has no words. So, someone who is quite severe, they might not have a second finding on this list, but that might be a patient that I might want to consider testing for, or might feel it's appropriate for.
- Janna Friedly: I also had a concern about that second bullet point. To me, in addition, it's just so vague that I am not sure sort of practically speaking how to operationalize that. I find that problematic.
- Sheila Rege: If you go to number 27, would that patient be covered, because that's covered with conditions? Single gene panels were not expected to yield a diagnosis. That would apply to your patient then?
- Amy Yuen: Some of my confusion is coming from the ands and the ors, as to . . .
- Gregory Brown: Right, so . . .
- Amy Yuen: . . . what combination you're using.
- Gregory Brown: . . . if I can clar-, yeah. If you can clarify, but it sounds to me like you need . . . if you need all of the first two pages, so slides 27 and 29, or two of anything on 29.
- Charissa Fotinos: I, again . . . we are not wedded to the exact language. That second bullet is indeed confusing, but if there is . . . we welcome . . . if the consultant has a better way for us to identify in what subset of children with global developmental delay it is appropriate, that was a challenge. 'Cuz, like I said, we have providers who are in it for kids who are a grade or two behind in school. That's not really the intent. So, if we can come up with language that allows for that condition you are describing, Dr. Yuen, then I'm happy to do that. We just didn't know how to come to that language.
- Gregory Brown: Well, that was kind of my . . . oh, go ahead.
- Female: [inaudible]

- Gregory Brown: Well, that is why I made a comment or had a question earlier, is it better to run it through medical geneticists and genetic counselors than to try and be prescriptive of all the things you can or don't want. I guess the flip side of that, my concern is, when you say if you've got a genetic counselor in Yakima, and their livelihood depends on having genetic results, or they get a rubber stamp every request from a physician in a community that . . .
- Female: [inaudible]
- Gregory Brown: . . . OK.
- Mika Sinanan: If we were to add the requirement for genetic counseling to the covered when at least two of the following are present, that would partially address your concern. So, it's genetic counseling and that list with whatever the right language is for it. You don't . . .
- Gregory Brown: If I read between the lines, your concern was people are, anybody with autism they're getting it, as opposed to more severe forms that have other . . . so, it's . . . and that's why you're trying to get this second issue in there. So, is there some way of . . . autism is a spectrum. Is there a way of grading it or, as you say, you know? More than x-number of standard deviations outside of development in a certain whatever.
- Mika Sinanan: It seems to me, we need to use as a forcing function the genetic counseling part of this anyway. Right? Before they get a diagnosis, because they will get the question about secondary findings and consent and all of that, which non-genetic experts will probably not do as good of a job as. So, if we include the genetic counseling here, then that's the filter. They have a genetic counseling, this autism or this degree of autism is likely to be genetically related or not, depending on the severity. Or this degree of delay is likely or not to be. I mean, I think it's at least one more filter.
- Kevin Walsh: I'd like us to be faithful to the process. We're wordsmithing a cover with conditions format, which is about eight steps ahead of where we are. So, I would like us to go back to sharing our feelings about what the evidence says, not what we wish was true about genetic testing.
- Gregory Brown: You raised the card unproven.
- Kevin Walsh: I agree with everybody's hopes for this technology, but hope is not what we're asked to make a decision on. I'm not all that impressed with the benefit of this testing, despite what our clinical expert has said. If all that is true, I wish it was reflected in the studies that people took the time to

- do. So, I don't feel that there is evidence that this is a technology that we can say works based on the evidence we're given.
- Seth Schwartz: Just had a question for you. When you say works, do you mean . . . are you doubting that it is a way to establish a diagnosis in some of these patients? Or are you more concerned about whether or not that matters?
- Kevin Walsh: As a primary care physician in a county where people struggle with resources, making a diagnosis alone is really an informational point. It doesn't always translate into a treatment point. So, I don't have as much invested in the benefit of making a diagnosis, per se, as other people do.
- Laurie Mischley: I'll just say as an alternative medicine provider, I see a lot of people who fall through the system. I feel like there is a burden on the system of people who are in search of answers that they're not getting elsewhere. So, I feel like I see a lot of those people. I do think that there is a benefit to the people in search of answers who have not been able to [inaudible] that can reduce [inaudible]. I don't think [inaudible] for somebody who doesn't come in with, you , their depression because of their NPHFR and their [inaudible] genetic genie. I mean, we do need to set some regulations, and I do think that there is a tremendous benefit here, if we write these regulations properly.
- Gregory Brown: Anybody want to make any last comment on efficacy before we move to safety in our discussion?
- Sheila Rege: Can we go and look at efficacy on what's been written? I got change in management. Change in medication, mortality, seizure control. We got benefit to families, psychosocial. Was there anything else that we said may be missing?
- Seth Schwartz: I think decreased resource use or something to that effect.
- Sheila Rege: Like NICU is what you were referring to?
- Seth Schwartz: Or just continued additional testing.
- Gregory Brown: Less additional testing. Less additional treatment.
- Josh Morse: I hate to interrupt. I'm gonna make sure I'm not doing it. Some of you are using the microphone, and it's not actually on, I think, if the red light's on.
- Sheila Rege: Oh, sorry.

- Josh Morse: No, I think, so Laurie, it happened to you a couple times. I think the buttons are hard to interpret. Thanks.
- Gregory Brown: OK. Safety.
- Sheila Rege: So, we have here on safety, misdiagnosis and psychosocial harms on the grid already.
- Janna Friedly: I just don't think there's any data at all.
- Gregory Brown: Did we hear anything about false-positive rates and stuff like that? I mean, it's mostly potential harm of . . . I mean, it seems psychological issues of, I've got this uncertain diagnosis. I don't know what it means or things like that, but, there didn't appear to be a lot of evidence on it.
- Tony Yen: That's my concern is, is that is there really any evidence that this actually works for a very diverse population? I think the standard . . . I really have no understanding of what the standard genome is composed of. Does it, will you . . . say you are someone from a subset in Africa, will you be compared to the standard genome? Is the standard genome really composed of, like, more of a Caucasian population? I really have no idea. Does it really identify people with diverse genetics?
- Amy Yuen: This is improving, but still, unfortunately, limited. So, there are a lot of databases of multiple people who have had genome sequencing so they can look at the different variants that pop up in people. It is skewed toward European Caucasian. It's improving, but that's still an area that needs continued improvement.
- Tony Yen: That actually speaks to the validity of this test for me. I suppose if you're European, Caucasian, the likelihood of this test functioning for you, as an individual, would probably be better. The performance would be better than someone outside of that racial group, I think, but this is kind of a guess.
- Amy Yuen: You could potentially have more uncertain variants in people of other ethnic backgrounds, because there wouldn't have been as many people of that ethnic background sequenced. There could be harmless variants that are more common in certain ethnicities, and you just wouldn't know that until more people are sequenced. So, people of different ethnic backgrounds could have a higher chance of an uncertain variant. Or of the pathogenic variant not being recognized as being pathogenic.

- Tony Yen: I find your comments really interesting, because it seems like we need to actually have more knowledge.
- Amy Yuen: Yes.
- Tony Yen: So, we're in the knowledge acquisition phase. Are we kind of ready to kind of release this knowledge and say . . . make judgments on this database that is still, I feel, in evolution, very much in evolution. That we're starting to make decisions on, oh, these are the genetic variants that are known to be pathogenic. These are genetic variants. We have no idea what these things might be. I feel like, I guess, the analogy would be that right now, we're kind of in that state where MRI is just beginning to outperform CT scans, that the resolution is getting to be improved over CT scans from a visual perspective. Then, we're beginning to see things. And we don't know what these things might be. The resolution is beginning to get finer, finer, and finer grained, but sometimes as we see more clearly, we still have no idea what we're looking at.
- Amy Yuen: The hope would be as more and more people are tested, that base of knowledge grows, and you have a more diverse group so that you can better understand.
- Gregory Brown: The other thing I think is that a lot of the safety issues, or this potential harm, is mitigated by appropriate before and after counseling.
- Female: Did we get clarification that there are enough genetic counselors in the region to . . . if we make that a requirement, that's not going to be a limitation?
- Gregory Brown: We don't have that data.
- Amy Yuen: That might be hard to figure out.
- Gregory Brown: To try to predict the demand and everything else, too, but, so, OK.
- Kevin Walsh: That's a great question, but as the discussion kind of evolved, we were talking about the potential of TeleHealth so that it doesn't require someone driving 200 miles to get the counseling. I mean, that can . . . I'm not sure we have the ability to really appreciate the current reality of where that's going. So, I'm not sure we should be including that.
- Gregory Brown: Anymore safety issue? Cost? We know what we're spending, but that's about it. We know what the test costs. We can say what we're spending, but that's about it.

- Kevin Walsh: We don't know what the package cost is, if we're talking about the importance of the genetic counseling before and after.
- Gregory Brown: Actually, \$28 or \$29 for 25 minutes, 30 minutes. So, an hour of counseling before and after is another \$120. So . . .
- Mika Sinanan: In terms of the cost question, one of the key issues is whether WES testing becomes the primary first step, as opposed to a later step. So, instead of step function through multiple prior testing, as I think was discussed and you alluded to, it becomes an earlier thing. So, when the cost studies pathway with earlier WES testing, we're more likely to be cost savings and pathways that used it later. Do you have an opinion about that?
- Amy Yuen: It depends a lot on the individual situation. In many patients, we may do some initial tests. Perhaps they might need a chromosome array, but if you add more additional tests, this gene test, this panel, those other in between steps, I think, start to add up more. So, moving to the WES early can be helpful, but it's not necessarily going to be best to do it first, depending on the situation.
- Mika Sinanan: So, for some situations, you would say, this really looks like that disease by the history, by the examination, by the phenotype. So, we ought to specifically test for that first. Then, if it's negative, then you move up to WES potentially, or other testing. In other situations, you say this looks like ten different things I could think of. Or, I've never seen it before, in which case that's the situation where you would go to WES earlier. Is that correct?
- Amy Yuen: Exactly. If we're looking at the patient and it is completely unclear, as to what might be the etiology, or we look at the patient and there are many, many genes that could be the etiology, then it becomes effective to go to the WES.
- Mika Sinanan: And does that testing sequence vary by their family history or appearance of any similar nature? I mean, does that, assuming their family hasn't been diagnosed.
- Amy Yuen: Exactly. So, you need that full medical history, their family history, their examination. You're going to bring all of that information into the decision making process. Certainly, if they come to see you in the clinic, and you find out a relative has had testing, we're going to say, OK. Let me get those test results and take a look at them first. Maybe your family already has an answer or a clue that can point me somewhere very specific.

- Mika Sinanan: But you wouldn't exclude the testing from anybody who had nothing in their family history to suggest a genetic basis.
- Amy Yuen: Exactly. In fact, many times, there is no family history, particular if you think about recessive conditions or genetic changes that occur de novo, brand new in that individual, you're not going to have family history in many of these situations.
- Mika Sinanan: Would the subtleties of that thinking be clear to a genetic counselor? Or would it require a geneticist?
- Amy Yuen: Oh, no. A genetic counselor would be very well aware of that. They are heavily trained in family history and inheritance patterns.
- Mika Sinanan: And are they licensed by the state? They're a state license . . .
- Amy Yuen: Yes.
- Mika Sinanan: OK.
- Amy Yuen: They are license by the State.
- Mika Sinanan: And they don't have cross state licenses. So, it's not . . . there's no national group necessarily.
- Amy Yuen: No. Not at this time. It varies from state to state whether licensing is available in that state.
- Sheila Rege: Follow up on that. What is interesting to me on the CIGNA coverage, which is included in the final report, I can't figure out the page. Here, it says 80, but they do say an independent board certified, a board eligible medical geneticist. They specify that a certified genetic counselor, but not employed by a commercial genetic testing lab. They go into the clinical nurses, genetic nurses also. Since we . . . I'm looking at our recommendation, is that something that we should consider. I understand the need for access, but a commercial genetic testing lab, now labs that are part of an integrated health system are excluded. I don't know if we can project this, Christine. I'm trying to figure out where, what page it is. Can you, on the final report? I can't figure out what page it is, but is that something we should consider when we look . . .
- Gregory Brown: [crosstalk] be able to find it.

- Sheila Rege: There it is.
- Gregory Brown: Yeah, page 59.
- Sheila Rege: Of the final report.
- Gregory Brown: Page 59 of the final report.
- Sheila Rege: Final report.
- Gregory Brown: So, I . . .
- Sheila Rege: So, when we're talking about cost, I wonder if we should put some safeguards in, or kind of what the committee feels is important is what I'd like to hear.
- Gregory Brown: . . . so, if . . . I want to make this discussion explicit and not have anybody reading between the lines. So, what I'm sensing or feeling is that there is a clear difference between a medical geneticist and a genetic counselor. I would say just give the healthcare history, someone with a Masters in genetic counseling and even not at a non-commercial lab, but in a community hospital or whatever, isn't going to tell a physician that no, you can't order that test. So, there needs to be some external guideline for genetic counselors. Is there a need for medical geneticists, because our concern is overuse of the test and cost. So, medical director thoughts? Expert thoughts.
- Amy Yuen: At Seattle Children's, they have their system of PLUGS. Genetic counselors regularly tell physicians, they'll call them up and say, I see your request here. Have you considered this other option? And they can and do stop tests from going out.
- Gregory Brown: And I believe that. And I think that's appropriate. And I think Seattle Children's is a very different environment that is . . . Dr. Rege said, is a genetic counselor sitting in Yakima by themselves with . . . because I grew up in South Dakota. It's a real community, and I know how things function. They're living in that community. They want to work with these other people. So, you don't want to be the reputation of I deny everything. So, again I mean, they're gonna say, yeah. I think that's reasonable. So, without some external guardrails of what's reasonable, that's why I see it turning into something as a rubber stamp. So, I don't have the knowledge to build those guardrails. PLUGS has already done it, but I don't know that we can say, we're gonna use the PLUGS criteria as a review, but maybe that's an acceptable approach to the medical directors. Then, it's a

dynamic thing. so, we're not saying this is the decision for the State moving forward, because PLUGS is going to evolve as things are learned and changed. Again, I'm just throwing something out, but clearly I'm sensing this concern about no guardrails on genetic counselors in particular.

Charissa Fotinos: I'm going to defer to Shana. She's the one that reviews all of these requests. So, she has a better sense of who is sending them, as to their appropriateness than I do.

Shana Johnson: I would say that the heterogeneity in regards to when these tests are ordered is very large. It's true if everyone took the approach of a well-trained academic tertiary care center, it would be less of an issue, but in reality, most of the requests are not coming from those facilities. They are coming from much more general nonacademic people that work very closely with labs whom they have a conflict of interest with. So, really tight guardrails are needed. Did that answer it?

Gregory Brown: No. Exactly. And again, I don't . . . well, just in terms of time, I don't . . . even with our expert, I don't think we can wordsmith and build those guardrails. So, that's why I'm . . . as you said, you're not getting these requests from someplace like Seattle Children's that's built this review committee. So, if PLUGS has a set of guidelines already in place . . .

Shana Johnson: They do, but the . . . so the trick is, and, you know, maybe this level of granularity is something that we do after a policy is made, because it is so granular. Their conditions are very helpful, but their conditions can still be applied either very liberally or very conservative. So, for example, they don't define what developmental delay or global development, at what level the WES is necessary. I can tell you Seattle Children's has never requested a WES for a mild global developmental delay, but if you read their criteria, you could read it that way. It says if they have that you could order it. So, they do have good criteria, but they are not well enough to define to consistency and not liberally.

Gregory Brown: Your recommended criteria say global developmental delay. You don't grade it. So, I mean . . .

Shana Johnson: Now, I think, wait, can you put those up. Can you show them to me. I don't think we . . . I think we excluded global developmental delay and uncomplicated autism.

Gregory Brown: So, we need to step back. I think we've had discussion on our three issues. I think it's time to vote again, but the pragmatic question, like I say, is how

are we going to draft something here in a timely fashion, but let's go to our tool.

Charissa Fotinos: May I add one thing? I was just talking to our boss here. One of the things we might be able to consider or think about as an agency is, could we fashion some sort of testing pathway that would only direct testing and counseling to centers of excellence that could be defined. That might be another way to put some boundaries on this, by being very specific as to where you can get counseling and testing, if you're considering this test.

Gregory Brown: Let's do our voting again. Let's see if we can operationalize something like that. OK. So, if we want to go to our . . . at the very end of our section, our tool is on page 5. First one is safety concerns. Do we want to add anything to the misdiagnosis or psychosocial harms?

Josh Morse: I have a process question for you? So, you, I understood you went through this vote previously? Are you addressing it again?

Gregory Brown: Well, so what Mika suggested is that we vote just as a way to see where people are at and start a discussion. So, that was a straw poll if you will.

Josh Morse: Gotcha. OK.

Gregory Brown: And so, this is the quote-unquote official vote is my understanding. Was that your suggestion? Yeah. So . . .

Josh Morse: Thank you.

Gregory Brown: . . . so, and since we did it in a different order, but for safety, outcomes . . . no. No. No. That's the end.

Charissa Fotinos: This falls under the psychosocial, and our expert mentioned it in terms of the life insurance policy, but I just want to say it goes even further with long-term care insurance and disability insurance.

Gregory Brown: OK. So, safety issues, again, compared to quote-unquote standard of care whatever that is.

Josh Morse: I'm going to count equivalent first, one, two, three, four, five six equivalent, and four unproven.

Gregory Brown: And on effectiveness, you added a couple of items, Sheila, that you wrote down.

Sheila Rege: [inaudible] Sorry, benefit to families, psychosocial, potential decreased resource use, and less provider shopping.

Gregory Brown: OK.

Sheila Rege: That's what I heard.

Gregory Brown: Any other effectiveness issues before we vote? OK. Vote on effectiveness.

Josh Morse: We'll start with more and some, one, two, three, four, five, six more in some. Hang on. Hold those up for a second. I think one more in all. Was that right, Dr. Yen? One, two, three . . .

Tony Yen: More in some.

Josh Morse: . . . oh, did you mean more in some? OK. Seven more in some, and three unproven.

Gregory Brown: And I think cost outcomes, I don't think there's anything to add here.

Josh Morse: Let's start with more in some. I see one, two, more in some, and eight unproven.

Gregory Brown: OK. So, we've got ten in each?

Josh Morse: Yes.

Gregory Brown: OK. So, with that, should we get our pink cards. We have cover, cover with conditions, or not cover.

Josh Morse: OK. I see ten cover with conditions.

Gregory Brown: Alright. So, now we're to where we were a few minutes ago. How do we operationalize this? So, the suggestion I just heard is that it's . . . this can be referred through a Center of Excellence that will develop testing pathways that can be approved by the medical directors, agency directors. Is that . . .

Mika Sinanan: May I ask before we do that, how do we . . . is there an official designation for a Center of Excellence? Or is it just self declared?

Charissa Fotinos: We're thinking that the places that we know do it well. I don't know if there are such things, but we could probably be thoughtful and work with

the institutes that do it well to come up with some criteria that we would want to see in a place that tested.

Gregory Brown: Has that ever come up before, Josh? We leave the agency to define the process? It's a circular issue.

Josh Morse: Yes. I don't think you can leave it to the agencies to define the process, but if you do make sure that it's done at a Center of Excellence with maybe a little bit more detail, that may be workable. The law gives you the authority to make the decision about the conditions and not the agencies. That's what the requirement is.

Sheila Rege: If you follow what the agency has come up with a cover of conditions, it's just . . . you have to think of all the ands. It seems fairly in line with some of the commercial insurance companies, the multiple congenital . . . the have to have all of the following, multiple congenital abnormalities effecting unrelated organ systems where single genetic tests are not expected to yield a diagnosis, where the constellation of clinical findings can be found in more than one genetically associated condition. The requirement of a medical geneticist or board certified genetic counselor with some safeguards about being employed by a commercial genetic testing lab, etc. No environmental exposures, and one more of the following is expected to occur, medication discontinued, initiated, care discontinued, palliative care. So, that seems . . . I mean, you've just got to read it through. That seems to take into effect what you had as a concern, it sounds like. That's clearer to me than . . . so that's cover with conditions . . . than the two or more with no . . . so I would like to see if I could get support for us as a committee, being OK with it as written by the agency director.

Mika Sinanan: May I make a suggestion, break it into two halves? The first half is the first set of potential, and the second half we would separately discuss, because they're . . . right?

Sheila Rege: Right. So, are we . . .

Mika Sinanan: We could vote on the first half and then . . .

Sheila Rege: . . . yeah, divide the question into the cover with conditions, as written by the agency directors and just discuss just that if we're comfortable with that.

Gregory Brown: So, we're eliminating page 29? Is that what I'm hearing?

Mika Sinanan: 27 and 28 slides.

Gregory Brown: Well, that's what I'm trying to understand. Are we . . .

Sheila Rege: We're going to talk about it next. We're going to see if everybody is comfortable with cover with conditions on this . . .

Mika Sinanan: 27 and 28.

Sheila Rege: . . . and then we can discuss this separately, as an addition, or whether we even want it, you know?

Gregory Brown: So, essentially, the first point on 27 is going to eliminate any adults? You're not going to get to be an adult with multiple congenital abnormalities. Well, I mean, essentially, but being unworked up or, you know? So, again, not never, but highly unlikely. So . . .

Mika Sinanan: So, primarily pediatric.

Gregory Brown: . . . I mean, in reality, it's only pediatric is I guess what I'm saying.

Sheila Rege: There is one condition. What is that condition where they get deep vein thrombosis hematomas?

Gregory Brown: The other question is, one of the examples that our vendor brought up was cancer. So, we're not doing this for any cancer oncology patients. Is that correct?

Female: [inaudible]

Gregory Brown: So, anyway, but I understand, but my point is, is inherited cancer isn't multiple congenital abnormalities. So, they don't meet the first and.

Charissa Fotinos: There are lots of genetic tests for which this is a useful test that don't meet the first and.

Gregory Brown: That's what I'm saying. So, I . . . that's my problem with this list. Again . . .

Female: [inaudible]

Gregory Brown: Well, right. And that's why I say, I don't know that we have the expertise to come up with all the appropriate uses of this test. We're saying we're

going to cover with some conditions. So, those some now have to be all the appropriate uses.

Mika Sinanan: Can I ask the medical directors, in the numbers that you provided, did those include cancer diagnoses?

Charissa Fotinos: None of the diagnoses that were reported were cancer diagnoses.

Mika Sinanan: So, there's a separate number? Or there were no requests for cancer diagnosis?

Charissa Fotinos: Do you know, Shana? Do you get requests?

Shana Johnson: Cancer was out of scope, but no. I don't get requests.

Charissa Fotinos: So, we don't get requests for cancer. I would see the tumor diagnosis piece as a separate and unrelated question to this at least in our consideration as agency medical directors.

Mika Sinanan: You're not looking at this coverage decision to include cancer patients. Is that correct?

Charissa Fotinos: No. No.

Mika Sinanan: OK.

Nedra Whitehead: Again, to clarify, there are inherited cancer syndromes that are tested not on tumors, but on actual blood or something, because those are what the example referred to and secondary conditions.

Charissa Fotinos: And those secondary conditions?

Nedra Whitehead: Yes. Yes. Well, I mean, those were within scope for the review.

Female: Tumors are the symptom of the genetic condition.

Nedra Whitehead: Yes. So, BRCA [inaudible].

Shana Johnson: Currently, the oncology providers are not asking for WES to evaluate for inherited cancer conditions. They are asking for things more in line with the NCCN guidelines. They typically do specific cancer related panels.

- Sheila Rege: I would echo that. It would be hard to do WES for that. I mean, that's why I asked about whether it affects FISH and BRCA and all that karyotyping. So, I don't see that.
- Gregory Brown: OK. But again, so is the first item on the top of 27 too restrictive for a lot of appropriate indications for WES?
- Amy Yuen: I think if we have to hit all of the ands, this would eliminate a lot of people that we would have normally felt were appropriate.
- Mika Sinanan: Can you be more specific about which ands are a problem?
- Amy Yuen: Particularly multiple congenital abnormalities, because you might have someone who doesn't have multiple congenital abnormalities, but they might have that profound global developmental delay, intractable epilepsy, something else that is not a physical anomaly.
- Sheila Rege: So, this is . . .
- Mika Sinanan: They may get to in a second part, which may be covered in the second part. Right? That's what . . .
- Sheila Rege: . . . right.
- Gregory Brown: Again, I mean, none of us are medical geneticists. We have an expert here, but again, I don't think functionally, it's just too detailed to come up with all reasonable scenarios to order WES.
- Mika Sinanan: So, my question is, to Josh, I thought you said that our role, that we were being asked to give you more detail than simply, let the agency figure it out. Or that if we said Center of Excellence is enough direction. Those are the two options we have?
- Josh Morse: Yes. And I've reached out for some support on the Center of Excellence. My sense is that's a little too broad. You can't delegate the decision making to the agency on the conditions.
- Mika Sinanan: So, they're asking us to be more specific than simply delegating it?
- Josh Morse: That's my suggestion. There's not a defined Center of Excellence. If you could point to a defined Center of Excellence and say, we like that one, then you have made that decision based on what you see. By saying it just too broadly without it being specific, then you have given that decision

making over to the agency. And we have had guidance in the past where the result is that is not a comfortable direction.

Gregory Brown: PLUGS is an example that we can point to is what you just . . . well, so for example, PLUGS is a specific entity with specific approach right now to review and approve testing.

Josh Morse: OK.

Gregory Brown: So, we could point to that example as a process by which the tests are evaluated.

Josh Morse: I think that would be better than not doing something like that.

Gregory Brown: OK.

Mika Sinanan: Then, of course, we've not seen the evidence.

Sheila Rege: I would like to see if our clinical expert . . . if we can project that CIGNA thing to see the clinical expert feels that is consistent with her practice. Again, that's page, I'm having trouble with this, page 59 on the final report. I'm going to give it to the clinical expert.

Seth Schwartz: Josh, I have a question. I think one of . . . my recollection is that one of our options is to convene a subcommittee to detail what the actual conditions are. I think we've used that very very infrequently. I'm not saying we give up just yet, but I think there is a third option. Is that correct?

Josh Morse: There is. If you look at your decision aid, I was just reviewing that, on page 4 there is a bit more detail about that. I don't know that you necessarily need to go to a full ad hoc committee based on the language here. We could bring back more information, but yes. I think there's other options.

Sheila Rege: But you can delegate.

Josh Morse: If you reach a kind of stopping point.

Janna Friedly: Simplistically, if you just removed the first and, would that suffice?

Amy Yuen: Yes, or even just moving that and item over to page 29 to that list of combination of two.

Josh Morse: I'm sorry. I don't understand what you just said.

- Amy Yuen: I'm sorry, slide 29. So, on slide 27, one of the first items in the list of ands is the multiple congenital abnormalities. So, if we take that out of the list of required and, and, and . . . and we moved that to slide 29 where there's the list of covered when at least two of the following, and put it into that list, and not make it be a separate and, but make it be one of the possible combinations, that would give a lot more flexibility, I think, for it to be used the way it needs to be used.
- Janna Friedly: I'm going back to the case of epilepsy without any other obvious structural abnormalities. To me, that still wouldn't fit within this covered, with at least two of the conditions. I don't see how epilepsy would be covered under that.
- Amy Yuen: Yes. I don't see it listed.
- Janna Friedly: So, that's where I still . . . I'm just wondering if you can just use 27 and 28 alone.
- Amy Yuen: Oh, and just take out the and?
- Janna Friedly: By removing the first and that would have enough guardrails with all of the other ands to be able to get at what we want. So, it's not condition specific but is really more that the constellation of clinical findings can be found, and there aren't any other explanations there, you've gone through the counseling and you expect that this is going to change management or . . . so to me, if you just remove the first and, it accomplishes what we . . .
- Mika Sinanan: The first and.
- Janna Friedly: Yeah, the first bullet point.
- Seth Schwartz: I would also say the final bullet point here should be the first bullet point here.
- Sheila Rege: I think it covers . . .
- Josh Morse: I'm happy to plug in and scribe this. Would you like me to start doing that?
- Gregory Brown: We're trying to get page 59.
- Sheila Rege: It's not in our packet so nobody can see it.
- Janna Friedly: I like this. This seems to . . . I like the intent.

Gregory Brown: So, let's just read it. Here, let me read it and so, this is the policy from CIGNA. It says one of the following. So, whole exome sequencing is considered medically necessary when disease specific criteria listed below are met, and when a recommendation for testing is confirmed by one of the following: 1) An independent board certified or board eligible medical geneticist. 2) An American Board of Medical Genetics or American Board of Genetic Counseling certified genetic counselor, not employed by a commercial genetic testing lab. 3) A genetic nurse credentialed as either a genetic clinical nurse or an advanced practice nurse in genetics by either the Genetic Nursing Credentialing Commission or the American Nurse Credentialing Center who is not employed by a commercial genetic testing laboratory who has evaluated the individual, completed a three generation pedigree, and tends to engage in post-test followup counseling. Disease specific criteria whole exome sequencing is considered medically necessary for a phenotypically effective individual when all of the following criteria are met. Individual has been evaluated by a board certified medical geneticist or other board certified specialist physician specialist with specific expertise in the conditions and relevant genes for which testing is being considered. WES results will directly impact clinical decision making and clinical outcome. A genetic etiology is the most likely explanation for the phenotype, as demonstrated by any of the following: 1) Multiple abnormalities effecting unrelated organ systems. 2) Known or suspected early infantile epileptic encephalopathy onset before three years of age. 3) Two of the following criteria are met, abnormality effecting a single organ system, significant intellectual disability, symptoms of complex neurodevelopmental disorder, or severe neuropsychiatric condition. 4) Family history strongly explained genetic etiology. 5) A period of unexplained developmental regression. Major point: No other causative circumstances, such as environmental exposure, industry infection, can explain the symptoms. Last one is clinical presentation does not fit a well described syndrome for which single gene or targeted panel testing is available.

Sheila Rege: I can screenshot it and send it to everybody. Would that help?

Gregory Brown: Any . . .

Sheila Rege: It's hard to . . . unless it's projected.

Josh Morse: That's the CIGNA policy. Is that right?

Sheila Rege: Yeah.

Kevin Walsh: Charissa, did you look at that policy, as you developed yours?

- Charissa Fotinos: I did. And I was just . . .
- Kevin Walsh: Can you indicate how it was . . .
- Charissa Fotinos: . . . trying not to plagiarize word for word.
- Kevin Walsh: Can you remark on how it was different?
- Charissa Fotinos: Um . . .
- Kevin Walsh: Or was it just . . . I mean, are the criteria the same as what you intended? Or is the wording, is it, is it beyond the wording?
- Charissa Fotinos: . . . I think it's probably just, no. This would . . . following this policy would accomplish the intent that we put forward. The three generation pedigree, I will defer to the expert as to the necessity of that. I really didn't see that in some of the information I looked at. I just lost . . . one second here. Let me pull it back up. So, no. I don't think it differs enough to be of concern to us.
- Mika Sinanan: So, a followup question, would it address the inappropriate utilization criteria you were referring to earlier?
- Charissa Fotinos: I think so, but I'll defer to Shana.
- Shana Johnson: Yes. Pretty much.
- Gregory Brown: So, we have agreed to take a break and reconvene. How about we take 10, 15 minutes to talk about this, make sure the medical directors don't have any concerns about this policy. I'm hearing this is what we're going to propose.
- Sheila Rege: I'd like to hear from the clinical expert some thought before we break.
- Amy Yuen: One of my concerns is with the bullet point of two of the following criteria are met. This might eliminate some of the patients that I would have considered it for, particular those ones who have the profound intellectual disability or delay, and don't have a congenital anomaly or something else.
- Gregory Brown: I'm sorry, what was the example.
- Amy Yuen: Two of the following. The second bullet.

- Gregory Brown: I understand, but what was your example?
- Amy Yuen: If I need to hit two of those, that might take out some of the kids with the . . . who have a very significant intellectual disability or delay but don't have one of the other symptoms.
- Sheila Rege: But wouldn't the bullet point clinical presentation does not fit a well-described syndrome? Wouldn't that . . . that's a 'or' . . . so that's . . . wouldn't that . . .
- Amy Yuen: Oh.
- Sheila Rege: . . . classify in that? Yeah.
- Amy Yuen: Circles 'or.' This is one of the things that is sometimes confusing with these is what is and, and what is an or?
- Sheila Rege: So, that would satisfy your concern then, that I can read.
- Amy Yuen: If they are or's, then that gives you flexibility.
- Janna Friedly: But they're not. Those two are and's.
- Sheila Rege: But it's on the bottom. No other causative circumstances. Then, the last bullet point, clinical presentation does not fit a well-described syndrome.
- Janna Friedly: Those are part of the . . .
- Sheila Rege: The or's.
- Janna Friedly: . . . no. They're and's.
- Sheila Rege: Oh, you still have it at two criteria, but one of the criteria is evaluation by a board certified medical geneticist.
- Amy Yuen: I think you have to hit all of those.
- Gregory Brown: Yeah. You have to hit all of the or's.
- Amy Yuen: From the way that it's written. And's.
- Janna Friedly: So, pick one of the following.
- Chris Hearne: So, what if we just change it to one of the following criteria are met?

- Amy Yuen: Oh, gosh.
- Sheila Rege: Oh, my gosh.
- Amy Yuen: We still need a few of those.
- Chris Hearne: A lot of the issues of over-utilization stem from people who are not specifically trained in genetics are ordering these tests. Since we've already included that caveat, then doesn't that take care of a lot of that issue? In my mind, it does, because if a non-specialist thinks somebody needs it, and a specialist thinks they need it, those are two very different situations in my mind. 4:15
- Kevin Walsh: The second bullet point under disease specific criteria isn't covered by your concern. So, or removes that requirement.
- Chris Hearne: Say that again?
- Kevin Walsh: Changing the wording from when all of the following criteria are met to any of the following criteria are met, because you're saying change it from and to or. My concern is that the second bullet point here talks about impact clinical decision making and clinical outcome, if you're saying or, then it doesn't have to meet that criteria. It can be just informational.
- Gregory Brown: He's just saying instead of saying two of the following, just any of the following. It's just that one line he's changing to any.
- Chris Hearne: The highlighted section.
- Laurie Mischley: Perhaps, Dr. Yuen just wants to add a bullet point for the specific population she feels is excluded? I'm just throwing that out there.
- Amy Yuen: I think the possibility of changing that word two of the following to any of the following would give the . . . Any of the following [crosstalk] organs, significant intellectual disability, family history, just that subsection.
- Tony Yen: Dr. Yuen, can I just ask you, are you performing this type of tests on just people with isolated severe developmental delay with no other findings at all? That they have nothing else, like . . .
- Amy Yuen: If it's profound.
- Tony Yen: . . . so profound developmental delay.

- Amy Yuen: So, severe profound. So, the . . .
- Tony Yen: No phenotypic abnormalities? No other behavioral abnormalities?
- Amy Yuen: . . . sometimes, they're just so profoundly delayed, but they don't have any other anomalies. So, the example that I would be thinking of, that 4 or 5-year-old who does not walk and has no words.
- Tony Yen: Are you able to define what you mean by profound?
- Amy Yuen: This is the part I think that becomes difficult because there's no precise scale. It's clinical judgment. So, that's where it becomes hard to apply this across the guideline here of different people ordering it.
- Tony Yen: But there's no specific measure to say a 7-year-old is profoundly delayed. There's no scale or some sort of objective scorings, methodology you could use?
- Amy Yuen: You could look at IQ, but not all of the patients would have necessarily had an IQ test or had one at an age where it's valid.
- Tony Yen: I think perhaps that's some of the difficulty over here is that what do we consider developmental delay, and . . .
- Amy Yuen: That . . .
- Tony Yen: . . . what is considered profound. And is it developmental delay to the sense that, oh, the person is not reading as quickly as my other one. Or is it that this person is not hitting milestones that would be expected at 3 years, 4 years, 5 years, their developmental milestones. Is there . . . I'm not a pediatrician, so I don't know these things.
- Amy Yuen: It's difficult, because you're right. We don't want to test the people who are mild. That's probably just the range of normal for people. You've got to have the whole range of people. So, we want to only look at people who are outside of that range. So, we don't want to test people who are just mildly delayed. There needs to be significant features.
- Tony Yen: I feel the clinical judgment of what's considered profound developmental delay is actually maybe the difficulty here, and if there is any way to subjectively measure that or to quantify it, perhaps we could have better guidance is the bottom line, if you can help us out? Or, I don't know if that's just, like, you're saying, like, ah.

- Amy Yuen: It is a little bit heard, because then you'd have to use more resources to have all the children formally evaluated, have an IQ score placed, or some objective number.
- John Bramhall: Do you think that there is a lot . . . this is a tough question. Do you think there are a lot of kids specifically that would benefit from this test that are not getting it, because of economic issues?
- Amy Yuen: Well, I think so. Yes.
- John Bramhall: I mean, thousands, tens of thousands, tens?
- Amy Yuen: That's a hard number to estimate.
- John Bramhall: Because, uh, the reason I ask is that the current . . . so, the coverage is, like, if there's something wrong with you, basically. I mean, not to be facetious, but it's very, very broad, and now we're disappearing down a rabbit hole of very, very specific set of concatenated requirements. That's only worth doing if we think that leaving the situation as it is opens the floodgates to a very large number of unwarranted tests, as these tests become more common. So, that's the basis of my question. Do you think there's an untapped pool of kids that should get these tests that are not, because they're not covered?
- Amy Yuen: There is a significant number, but it's very hard to estimate how big that is.
- Chris Hearne: I think setting any sort of criteria for who gets . . . clinical criteria . . . to me, saying two of the following are met, that's arbitrary. We're not basing that on anything other than some underlying desire to limit them out of testing. To me, I'm very comfortable saying if somebody is trained in genetics and making this decision, then it's an appropriate test. Trying to put specific criteria for who can and can't get the test, we're not going to be able to do that. Even if we could, it might be obsolete in a year or two years, because this technology is changing.
- Sheila Rege: So, my worry with that is, I have friends who say this kid is not progressing like my older kid. So, would every kid go to a . . . there'll be a telehealth geneticist who approves every test and is very popular on Yelp. So, that's my concern with that, because I think we . . . it's children, and not defining profound developmental delay is an issue. It's subjective.

- Chris Hearne: What I hear from the agency medical directors is that we're not getting a lot of sort of frivolous test requests from . . .
- Charissa Fotinos: We are. That's part of the problem.
- Chris Hearne: From geneticists and genetic counseling?
- Shana Johnson: No. That's not true either, but there's only . . . it's a big issue across the board. Seattle Children's does an amazing job. I'll leave it at that. It's a big issue. Telemedicine ordering WES on everyone with an abnormality is a reality and is already happening. That reality could be they think their joints are too mobile, and they order a WES. That's a real example.
- Gregory Brown: But again, that's coming from a medical geneticist doing telemedicine. There are a lot of conflicts of interest in this space.
- Nedra Whitehead: I think one of the things that we don't know but wonder about is the financial gain that someone might get from ordering the test.
- Charissa Fotinos: You can apparently, and I don't know if Josh . . . oh, Josh is in the room. We can be asked to take another look at this and look at things like what a Center of Excellence might be and bring that to you. So, we can, apparently do something like that if that would be helpful.
- Gregory Brown: Again, I view our role as helping you. So, if you're . . . if we feel it should be covered in some conditions, we don't feel, but we have the . . . so I don't know if it's an ad hoc committee or if it's just waiting for a report back from you, but I think that's the appropriate action. I agree.
- Mika Sinanan: So, let me suggest that they give a first pass at either the Center of Excellence or incorporating something that captures the sense of the discussion but doesn't artificially limit in the ways that we've just talked about, and that be brought back to a subcommittee that prepares it for at the next meeting. Then, we just bring it forward to the next meeting that topic.
- Sheila Rege: I second that, if that is acceptable.
- Gregory Brown: I just have a simple question. So, is there . . . are there ICD10 codes for profound developmental delay? Is it just developmental delay or nothing? Or is it graded?

Amy Yuen: It is specifically if you look at the literature, global developmental delay is very specifically defined as being greater than two standard deviations of abnormality in multiple realms.

Gregory Brown: So, again . . .

Sheila Rege: How do you measure that though?

Shana Johnson: There are a lot of pediatric tests that are standardized and validated that measure that. I don't know about in kids who are less than 2, but in the 2 to 6 range, there is neuropsychiatric and psychiatric testing to evaluate all of that with norms and normal distributions.

Gregory Brown: . . . right. So . . .

Seth Schwartz: It might be challenging to apply in a NICU setting.

Gregory Brown: . . . well, no, again. So, I heard a suggestion that we . . . the vote of the committee is to cover with conditions, based on a Center of Excellence concept, and we are returning this to the medical directors, agency medical directors to better define what that Center of Excellence is. Is that what you're requesting or asking us? Again, I feel like we're . . .

Shana Johnson: I have a plan.

Gregory Brown: OK. So, is that something we can then vote on for that recommendation? Is that specific enough of what we're asking back from the . . .

Josh Morse: You're not asking for an ad hoc group. You're asking for more information to be brought back at the next meeting.

Gregory Brown: Yes.

Josh Morse: OK.

Gregory Brown: OK.

John Bramhall: Sorry, while we're here . . . not to persevere about my comments before, but the 2018 numbers here, about 90 cases apparently that have been funded. So, is it the case . . . I don't know if you can speak freely. Is it the case that you think that some of those cases you can't defend against in the scientific opinion, in your opinion, they're frivolous, and there's no mechanism at the moment to defend against those claims.

- Shana Johnson: Currently, it's on prior authorization. So, they're only approved if they meet criteria that are currently very similar to Seattle PLUGS and CIGNA's policies. So, those are case . . . but what's happening is, we're getting more and more requests for cases that don't meet that level of medical necessity.
- John Bramhall: So, you already have an algorithm for determining a decision about prior authorization?
- Shana Johnson: Yes.
- John Bramhall: And that algorithm looks similar to the . . .
- Charissa Fotinos: But you're recommending to us your thoughts allows us to publish that and make that frivolousness stop in a different way.
- John Bramhall: So, the suggestions that you've made are not ex cathedra statements. These are based on real world problems that you're encountering.
- Shana Johnson: Correct.
- John Bramhall: OK.
- Shana Johnson: That's why this topic was brought to the committee.
- John Bramhall: Sure. I understand that.
- Gregory Brown: We vote on approving is that we are voting to cover with conditions. And we would like the agency medical directors to come back with Center of Excellence criteria for what those conditions are, or the guidelines for what those conditions are. Is that a fair statement.
- Mika Sinanan: Sorry. I'm not clear. Are you . . . there are two ways to look at this. One is, what's a definition of a Center of Excellence so we can define a set of those around the state. The second is, what would a Center of Excellence choose to use as the criteria? So, which one are we talking about?
- Janna Friedly: I was thinking the second.
- Mika Sinanan: So, there would be a set of criteria. I think that will help be the filter for people before they even order it to look at and say, is it appropriate or not, as opposed to sending patients 100 miles to another place.

- Janna Friedly: What I worry about with using a strict Center of Excellence is that you are then funneling all the patients through that Center of Excellence. That may create access issues, unintended access issues, but if what you're trying to do is to really just wordsmith the criteria to sort of make sure that it meets the spirit of what we have been discussing, then that's different to me.
- Sheila Rege: I like that.
- Mika Sinanan: It's the criteria that I think we should be working on.
- Gregory Brown: So, give me a motion.
- Mika Sinanan: The motion is that we have voted for a set of conditions. We are asking the medical directors to come up with a draft set of criteria based on this discussion and based on the samples that we've looked at that appropriately address their concerns about inappropriate use, but also allow appropriate use.
- Seth Schwartz: Second.
- Gregory Brown: And since we're not adopting a final policy, do we need our ten minute cooling off period to vote? OK. All in favor?
- Group: Aye.
- Gregory Brown: Any opposed? OK. We will hear back from the agency medical directors on what criteria they recommend. Thank you. Lunch, and we are . . .
- Josh Morse: So, before we go to lunch, I would like to say thank you now midday while we have everybody here. That may change as the day goes on. Thank you, very much, for your time and your service, and I will miss our mornings together before these meetings. That's for sure.
- Gregory Brown: Thank you.
- Josh Morse: Thank you. You've done a great job.
- Gregory Brown: Thank you, very much. It's been an honor and a pleasure to serve here. Yeah. When you called me a couple years ago and said, would you be interested in the job, I turned you down, and then I came back and changed my mind. So, it was probably the changing of my mind that I've had in a while. So, thank you. It's been a pleasure.
- Gary Franklin: Have you decided on what kind of cowboy boots you're going to get yet?

Gregory Brown: I've already got them. I've got a picture if anybody needs to see the pictures.

Mia Hagen: . . . finally faculty at the University of Washington. I'm an assistant professor. I am also the director of our clinic at Husky Stadium for sports medicine and one of the team physicians for the Huskies. My clinical practice is primarily lower extremity sports medicine, which 50% or so is hip preservation. Then, the rest is complex knee mostly, a little bit of shoulder, and I am now in my third year of practice. So, I finished my board certification over the summer.

Gregory Brown: Welcome. Thank you.

Mika Sinanan: Should we go around again, since he wasn't here for our earlier [inaudible]?

Gregory Brown: Sure. So, Mia, you know me, orthopedic surgeon, Tacoma, Washington.

Sheila Rege: Radiation oncologist eastern Washington.

Seth Schwartz: I'm a neuro-otologist at Virginia Mason.

Chris Hearne: I'm a nurse practitioner. I work with Swedish.

Tony Yen: I'm a hospitalist at Evergreen.

John Bramhall: Anesthesia guy a Harborview.

Laurie Mischley: Naturopathic physician and do Parkinson's research.

Kevin Walsh: Family medicine, Community Health of Central Washington in Ellensburg.

Mika Sinanan: Across the road doing general surgery. Thank you for taking care of my patients.

Gregory Brown: It looks like Dr. Johnson got the discussion.

Shana Johnson: Yes. I did. We're just waiting one second to get the presentation up. While they're working on that, I guess I'll just introduce myself. So, I'll be presenting the agency medical directors' comments on the FAI policy. I'm a physical medicine and rehab physician. I work at the Health Care Authority supporting the Medicaid program.

Alright. It looks like we've got the presenter working again. Josh, are we ready to go?

Josh Morse: Yes. I apologize.

Shana Johnson: No.

Josh Morse: It's always difficult with the technology.

Shana Johnson: Alright. So, today we are relooking at femoroacetabular impingement. We first looked at this topic in 2011. We subsequently did horizon scans for literature updates that could change our previous decision in 2016 and 2018. At that time, new studies that might change our previous decision were identified. So, it was selected for rereview.

Back in 2011 when this was selected, the committee found that hip surgery for FAI is not a covered benefit, therefore, not medically necessary.

So, following my presentation, the evidence vendor will talk and give an overview of all the details of the entire body of the evidence. My presentation, I'm really just picking out a few pertinent points that I think will be relevant when talking about what an appropriate clinical policy would be for this decision. So, one of those relevant details is how we're defining femoroacetabular impingement syndrome, how we're defining it.

The highest quality studies I saw in the evidence review, as well as the evidence vendor in regards to how we're defining this was the Warwick Agreement from 2016, which is defining FAIS as a combination of symptoms, clinical signs, such as restricted range of motion, positive impingement test, and radiographic findings of CAM or pincer morphology on radiographs.

Next slide is just to give you kind of a more detailed picture of what we're talking about. Picture A is normal morphology. Picture A is showing cam morphology, which results in premature contact of the femoral head with the acetabulum, and pincer morphology with overgrowth on the bone noted in letter C.

Another pertinent point from the literature that I thought was relevant was that the prevalence of asymptomatic femoroacetabular impingement is high. About 20% of the general population, this morphology change is observed; however, only a subset of those people develop pain and/or

symptoms. The high rate of its asymptomatic occurrence makes it more complicated to understand and treat as a distinct pathologic entity.

Next, I want to shift to kind of talk about, from a policy and agency standpoint what our concerns are. From a safety standpoint, our concerns are medium in regards to, this is a safe intervention. This is an intervention that improves health outcomes and is effective. Efficacy is high. The cost concern is high, as well.

So, current state agency policies for femoroacetabular impingement across the state agencies including PEBB, Medicaid, and Labor and Industries are that it is to be implemented based on the Health Technology Clinical Committee decision, although admittedly, it's not consistent across the Medicaid managed care programs at this time.

During these presentations, we like to give you a sense of the utilization data and what we're seeing with that. Not surprisingly, because it had a not cover determination, there is very utilization data over the past five or so years, since the decision.

Another important factor we look at when we're looking at clinical policy is kind of a landscape overview of how other payers are looking at this intervention. The centers for Medicare and Medicaid services do not have a national or local coverage determination. Pretty broadly across private payers, they do have a cover with conditions policy. Their policies tend to be fairly tight, and they tend to have pretty similar conditions across all private payers in the report.

So, the evidence vendor pooled the data and looked at the evidence body as a whole. I did want to point out and discuss two studies that I thought were particularly well done with good quality and some of the pertinent findings from those that I think may have an impact on the committee's decision. So, the first paper was by Palmer, arthroscopic hip surgery compared to physical therapy in the treatment of symptomatic femoroacetabular impingement. For their primary outcome measure, they used the HOSADL, which is a validated outcome measure for use in active young adult. So, it was a good choice of measure. They have a prespecified minimum clinically-important difference that they used. They did meet that difference at 9 but with a Y confidence interval. Their outcomes were fairly short-term at 8 months. Overall, the study's risk of bias was quite low and quite well done compared to other papers I've seen in this area.

A couple of other important points from this study were looking at the percent of patients that met the MCID and the HOSADL score in this surgery arthroscopy group compared to the physical therapy group. It was 51% in the surgery versus 32% in the physical therapy group. As far as achieving a pass score of greater than 87, it was 48% in the surgery group versus 19% in the therapy group.

One of the limitations of this study that I'll be very interested in hearing our expert's opinion on is the heterogeneity of the surgical interventions that were performed in this study. More specifically, the majority of the patients had a labral repair or a labral debridement. I didn't see any subanalysis that just looked at people with hip impingement with the bone morphology change. So, that is important to note, since labra repairs can cause mechanical symptoms. FAIS, as described by the 2016 Warwick Agreement notes impingement of mechanical symptoms from purely bone morphology. This study appears that it has both those populations in the trial. So, there is some question, were the surgical interventions too heterogeneous to judge the effectiveness of FAIS based on bone morphology changes alone.

The second trial was the Griffin trial. Again, this is a nicely done study. It was a multicenter randomized controlled trial. Their primary outcome measure was an iHOT 33, another validated functional outcome measure in a young active population. Of note, the patients in this study had symptoms for at least three years before they had the intervention. They met their minimum clinically important difference. Reading in the paper, however, about 70% of these patients also had some sort of labral procedure completed.

So, when I look at the evidence report as a whole, the pertinent limitations I see is that the asymptomatic presence of FAI is high. As the evidence vendor will go into more detail during their report, a high quality definition of FAIS as a distinct entity is unclear based on the literature. The key studies, most had a procedure to address a labral injury, which also would cause mechanical symptoms. So, it wasn't clear if the evidence was generalizable to FAIS just based on bone morphology changes. On the other hand, the Palmer-Griffin studies were two very well-done randomized control trials that both met their prespecified validated functional minimal clinically-important differences, and their studies did support hip arthroscopy with mechanical symptoms. Most of those patients had a labral pathology.

So, next, I'm gonna tell you why that matters. So, it matters because our current policy is that we do cover diagnostic hip arthroscopy if you have

mechanical symptoms, and you have failed conservative care and you qualify for surgical hip arthroscopy for repair of that labral injury or a loose body or osteochondral lesion. What our policy currently doesn't cover, based on the 2011 decision is reimbursement for treatment of the cam or pincer lesion. So, looking at two sides of this. On the one hand, hip impingement is a clinical diagnosis based on mechanical symptoms, and the patients included in the trial met that clinical picture. The key studies showed that those patients benefited functionally meeting their prespecified NCID in studies with a low risk of bias, although imprecise findings. On the other hand, hip impingement from cam and pincer morphology is unclear, as a distinct entity. It has a high asymptomatic presence. I didn't see any studies, or any subset analysis that actually looked at hip impingement from these bone morphology changes and the results of hip arthroscopy from them. If I missed that in the literature, let me know. Our current policy does cover arthroscopy for mechanical symptoms. We just don't cover the treatment of the bone in the cam or the pincer lesion due to the uncertainty of it being a distinct clinical entity and the distinct treatment of it resulting in approved outcomes. So, when agency medical directors looked at this evidence as a whole, they were not compelled that FAIS, as defined in the Warwick 2016 Agreement with solely bone morphologic changes benefited from hip arthroscopy. They, therefore recommended that hip surgery for FAIS is not considered medically necessary. So, that's all.

Kevin Walsh: Do you have a sense of the percentage of people who get this surgery in this state who are over the age of 40 or 50? I mean, do you have an age range?

Shana Johnson: That's a great question, and going into this topic, that was one of our biggest questions was if age was a differentiator for this surgery. The aggregate will go into the findings on that in more detail, but in essence, the findings were mixed. One of the key RCT's showed an age effect, and the other did not. So, it was not consistent across trials of those over 40 versus those under 40.

Kevin Walsh: It just causes me to wonder about the applicability of the studies that you've cited who are all done on younger people.

Shana Johnson: They were not all done on younger people.

Kevin Walsh: I'm sorry. I misunderstood you then.

Shana Johnson: Oh, what I maybe said was that the outcome measure they used was a good one, because it was sensitive for changes in those who are active,

young individuals. I was speaking to that . . . they chose a good primary outcome measure. Was that where you got, perhaps?

Gregory Brown: I think what she may be saying is, most outcome measures for the hip were developed for hip arthritis. So, they have a lot of healing effects when they're applied to the younger, athletic, active population, but younger are not necessarily young. So, I'm guessing that's what you're trying to express?

Shana Johnson: That was correct.

Mika Sinanan: Does this recommendation have any effect on the clinical policy around diagnostic hip arthroscopy or surgical arthroscopy that you referenced?

Shana Johnson: I'm sorry. I missed that with the cough.

Mika Sinanan: Would it have an effect on the other two policies, the diagnostic and the hip arthroscopy policies?

Shana Johnson: So, this would have an effect on this . . . so, where this falls into line is the surgical hip arthroscopy policy. That currently, did I go past it? So, if it was chosen as effective, in addition to seeing labrum tear, joint exploration, you would also see the procedures performed specifically for cam and pincer lesions. I think one of the names is femoroosteoplasty? The name of the procedure where they shave the bone? Those would be listed in there as reimbursable, too. In other words, two codes, 29914 and 29915, would be added to the surgical hip arthroscopy policy.

Mika Sinanan: But if it wasn't covered, everything else that's included in that statement would still be covered?

Shana Johnson: Correct.

Janna Friedly: Would now be a good time to clarify some of these points in your presentation?

Shana Johnson: Yeah. I think so.

Mia Hagen: So, I think it's important to understand the role of the labrum in the hip and how to really define FAI in relation to labral tears, because that seems where a lot of the confusion . . . an area where there's a lot of confusion. So, the labrum is a fibrocartilaginous ring around the hip joint that has several functions to help preserve the suction seal of the hip joint by increasing service area. It helps to lubricate the cartilage and thus provide

nutrition to the cartilage. The labrum, itself, does have a lot of pain fibers on it. So, if you have a tear, you can have pain; however, labral tears are very common. They are a normal part of aging. When they happen when you're younger, there is usually a reason why it happened. So, there are a number of causes for why people get labral tears, one of which is FAI, or FAIS. So, when you have bone impingement between the femoral head/neck area and the acetabulum, you get a very characteristic type of labral tear in the area of that zone of impingement. So, if you were to only repair the labrum without removing the underlying cause for the tear, the labral tear recurs, and patients need revision hip arthroscopy. So, that has been shown in multiple studies of why people might not do well after a labral repair. They have found that if the bone wasn't corrected, they tend to have recurrent symptoms. If you correct the bone, they get better. Other causes for labral tears are things like hip dysplasia. So, if you have under-coverage of your socket, you have increased surface area, earlier wear in the joint, and you can also develop a labral tear. Obviously, a hip arthroscopy is not a good way to treat dysplasia, because we have no way of putting new bone on the socket to increase coverage. So, it's generally contraindicated in patients with dysplasia. Similarly, as I mentioned, labral tears are often just a normal part of aging. So, if the underlying cause for your labral tear is that you're getting older, most likely, cartilage isn't as good in the hip joint, as well. So, if you do a labral repair on someone who is older and ignore the fact that they are missing half of the cartilage of their hip joint, they are also not going to do well, because their underlying problem is arthritis. So, it's really important to understand why people are getting labral tears. If you think someone has a symptomatic labral tear, and then to address the underlying thing that is causing their tear. So, that's why it doesn't make a ton of sense to me to only approve labral repair without approving the underlying bone morphology that might have predisposed that patient to that tear, especially in keeping with the current literature showing that doing the labral repair without correcting underlying bone morphology leads to high rates of failure of hip arthroscopy. Does that make a little bit more sense, in terms of that relationship between the two?

Shana Johnson: I think it does make sense. I also think that the evidence vendor will present that. Not everybody sees it that way. That's why it's controversial. We certainly appreciate how controversial it is, which is why this is such a good forum to talk about this and to have you here and bring that perspective. So, I really appreciate you bringing that side. We certainly talked back and forth, well, but the reason they got the labral tear is because they're impinging. So, you don't want to wait until they're tearing up their hip before you intervene, but then it became circular where there's a camp that says, but we're not convinced that this is even a thing,

because the natural history studies are actually quite mixed, as far as showing this as a distinct pathologic etiology, but that said, that's what the evidence report and the evidence vendor's findings will go into more detail about that. I think that is the crux of the issue. If you accept that this is the first step in a bad process, then of course, you would have that covered and approved as part of the policy, but if you don't accept that as the process, it's not as straightforward. So, that is where our clinical question falls is exactly what you said. So, thank you for bringing that up just right on the get-go. That's the issue.

Laurie Mischley: Can I ask a clarifying question to the expert? It seems like there are two, maybe two different pieces to this. One is if you're going into someone who has a labral tear, and at that same time you see there is a cam or pincer lesion, and that's the only thing that leads you to believe that that might be important to correct so that doesn't recur, that's one thing versus saying someone has a cam or pincer lesion. We don't want them to develop in the future a labral tear. So, we're gonna go in and fix that. Which of those two are we saying?

Shana Johnson: So, these studies, everyone had mechanical symptoms clinically. So, they were symptomatic. So, I think based on the study's methodology, when the surgeon went in for the hip arthroscopy, they kind of decided what was the best procedure for that patient. If they were impinging, that's where the surgical intervention slide came from. It kind of talked about what they most commonly saw and what they most commonly did. Does that answer?

Gregory Brown: If I may, Mika, when was the last time you did an exploratory abdominal operation?

Mika Sinanan: Oh, I don't know, 15 years ago.

Gregory Brown: Right. So, I don't think any of this is exploratory hip arthroscopy? With the imaging that we have, if you don't have imaging ahead of time showing a pincer or cam lesion, you're not going in to see what you find and decide what you do when you get in there. So, I think that's a misconception. So, but again, that's just my personal comment on the discussion right now. Let's go . . . I think we're public comment next, and we're a little behind. So, do we have anybody sign up for public comment? We did not? OK.

Josh Morse: We did not have anybody sign up in advance.

Gregory Brown: OK. And is the line open or unmuted? OK. This is Greg Brown. I'm the Chair of the Health Technology Clinical Committee. We are reviewing hip

surgery procedures for treatment of femoroacetabular impingement syndrome. We are wondering if anybody is on the line and would like to make a public comment? OK. I'm not hearing anybody, so you can mute the line again. Let's have our evidence report. Then we'll continue our discussion and questions after that.

Erika Brodt: OK. Alright. Can you hear me? OK. Hi. My name is Erika Brodt. On behalf of AAI, I'll be presenting our results of the rereview of femoroacetabular impingement syndrome. The purpose of this report was to update the 2011 Health Technology Assessment by systematically reviewing, critically appraising, and analyzing newly available published evidence on the safety and efficacy of operative treatments for FAIS with the focus on the comparison with nonoperative treatments. Key questions one and two from the original report, which asked about a case definition for FAIS and the validity and reliability of that definition, as well as outcome measures were updated as contextual questions for this report, and as such, we are not subjected to the same formal systematic review process.

Brief background here. FAI or FAIS is a relatively recent discovery. The original description is credited to orthopedic surgeon, Dr. Reinhold Ganz, who first proposed the condition as a cause for hip osteoarthritis in a 2003 publication. Advances in equipment and technique over the past 10 to 15 years have contributed to an increase in the number of hip arthroscopy procedures performed worldwide, and have made it one of the more common treatment options for symptomatic FAI.

So, femoroacetabular impingement is a condition in which extra bone grows along one or both of the bones that form the hip joint, so the proximal femur and acetabulum, giving the bones an irregular shape. Because they don't fit together perfectly, the bones rub against each other during movement, particularly flexion and internal rotation. This abnormal contact is thought to eventually compromise the labrum and cartilage of the joint and possibly lead to osteoarthritis.

Gregory Brown: We all have a folder with your presentation. So, why don't you keep going? Or is not in front of you?

Erika Brodt: Sure. OK. I can do that.

Gregory Brown: Unfortunately, we're a little behind, so . . .

Erika Brodt: Yep. No problem.

Gregory Brown: If we lose our slides, keep going, and we'll follow in our books.

Erika Brodt: OK. So, I'm on slide 5, the classification of FAI. It just shows you that there are three types of FAI, cam, pincer, and combined or mixed type impingement. In cam impingement, the femoral head is not round and cannot rotate smoothly inside the acetabulum. Here we go. Now, this is not moving forward. So, you can see the picture in the presentation. The middle picture shows cam impingement where you see a bump on the edge of the femoral head that leads to abnormal contact with the acetabulum. Pincer impingement occurs because extra bone extends out over the normal rim of the acetabulum, causing premature contact again. There we go. OK. And then, combined or mixed type impingement just means that both pincer and cam types are present. Diagnostic criteria has historically relied on radiographic parameters to look at these variations in bone morphology. We'll talk more about that in the contextual questions.

So, real quick, a little bit of terminology. Since the previous report, work has been done to further define the clinical presentation of FAI. I think it's already been talked about a little bit. To that end, the term FAI syndrome, or FAIS was proposed by the authors of the 2016 Warwick Agreement, which is an expert consensus statement on the definition and treatment of FAIS. The intention with this terminology is to emphasize that symptoms, clinical signs, and relevant imaging signs need to all be present for a diagnosis. That's in order to distinguish it from asymptomatic FAI or radiological FAI that may be more descriptive of HIT morphology versus a clinical disorder, as the authors refer to it. So, when we talk about FAIS in the report or here, we are referring to patients who have symptoms.

Mika Sinanan: Can I ask a question? Before you move on, what proportion of hip pain is represented by patients who carry this diagnosis? I mean, is it small, 50%, or?

Erika Brodt: I do not know the answer to that question.

Gregory Brown: I can't tell you how many patients I see in clinic with hip pain that it's from their low back. So, when you say hip pain, you know? I mean, or trochanteric bursitis that has nothing to do with the joint, or whatever.

Mika Sinanan: Is this a rare diagnosis in the global scenario of hip pain? Or is it a common diagnosis?

Gregory Brown: Increasingly common. I mean, I . . .

Erika Brodt: Yeah. I think it's hard to really . . . there aren't great, like, epidemiological studies saying what percentage of, like, the whole total population of hip

pain, which percent is FAI and labral tear? Hip pain is extremely multifactorial. Aside from just hip impingement and hip arthritis, you can also have things that are external to the hip joint that refer pain there. You can have a number of soft tissue problems, like, flexor tendonitis, a core muscle injury, adductor tendonitis, etc. There is referred pain from the GU area, as well. So, it's really multifactorial. The classic presentation of FAI with the labral tear is pretty specific, in terms of what causes pain and what the limitations are in motion, as well as where they're experiencing their pain, but I would say it is . . . it's . . . the morphology is common, as was presented in the previous slides. Whether or not someone is symptomatic from it is not necessarily as common. I think there is a lot of understanding of how people experience pain related to it that we don't have yet.

Mika Sinanan: Thank you. So, if a patient comes in, you said, the combination of the kind of pain, the circumstances of the pain, and your physical examination that says, ah. They may have FAI. We need to do x-rays? Or do you just say they have pain. Let's do the x-rays and then you make the diagnosis of FAI?

Erika Brodt: You need to have the underlying morphology, as well, to meet diagnostic criteria for this.

Mika Sinanan: Do you suspect it on the basis of their history and physical examination? Or is it just pain?

Erika Brodt: It, yes. There is a very specific type of way it would present, typically. So, then, yeah.

Mika Sinanan: What would that be?

Erika Brodt: So, pain in the anterior groin or C-sign distribution associated in particular positions of impingement, of which most commonly is flexion, adduction, and internal rotation of the hip joint. Sometimes, also external rotation, as well as restriction in range of motion, particularly internal rotation and 90 degrees of hip flexion. OK. Any other questions?

Gregory Brown: So, we do need to be ethnically and culturally sensitive, I think. I think we're not being culturally sensitive. So, for Dr. Bramhall, I think this is the Warwick consensus. So, OK. The second W is silent in the British pronunciation.

Erika Brodt: I've been saying it wrong this whole time. Thank you. Warwick. Oh, my goodness. I'll have to try to remember that now.

Gregory Brown: Who said orthopedists didn't get cultural sensitivity training?

John Bramhall: Orthopedics has an A in it as well?

Gregory Brown: Exactly, just like pediatrics.

Erika Brodt: Alright. So, the overarching goal of treatment for FAIS is to reduce symptoms and return patients to their activity or sport. A variety of nonoperative and conservative approaches have been described in the literature, and that includes things that are more passive, like, education, watchful waiting, analgesics, steroid injections, lifestyle and activity modification to more active actions, like, pelvic postural retraining and exercise rehabilitation, and manual therapies. The specific goals of the latter are to improve hip stability, neuromuscular control, strength range of motion and movement patterns. Operative treatment of FAIS is performed via arthroscopy primarily, and open hip dislocation. The prior report also mentioned a mini open approach, which is, like, a combination of these two, but that's rarely done in current practice anymore, and I think only two case series included that in our report. The goal of surgery is to correct the morphological variations in the femur and acetabulum and to repair existing labral tears or damaged cartilage, and to achieve impingement free range of motion.

However, there is no agreed up evidence based standard approach to either surgical or exercise physiotherapy based treatment for FAIS. Two recently published documents provide guidance regarding the treatment of FAI and FAIS, but they acknowledge the lack of high quality prospective and comparative data on which to base a definitive treatment for FAIS. The authors of the Warwick agreement mentioned previously, and I'll discuss further in the contextual questions as well, suggest that the decision making process should be from a multidisciplinary perspective, especially in secondary and tertiary care, in which all treatment options are considered. The second document is a recently published consensus or best practice guideline for arthroscopy that builds on the Warwick agreement actually and provides pre, intra, and postoperative recommendations, as well as contraindications, in an attempt to decrease treatment variability. Three months of nonoperative care is recommended prior to surgery with some exceptions depending on activity level. Similarly, there is no consensus regarding a standardized physiotherapy and/or manual therapy regimen for the treatment of FAIS. Details of what should be incorporated into such a program have not been well tested and are not well described in the literature.

In this report, included RCT's of interest, all compare arthroscopy with an individualized, supervised, physiotherapy based rehab program, but the specific therapy components and the frequency in number of treatment sessions differ, as I'll show on the slide coming up.

So, here is where we talk a little bit about the asymptomatic prevalence in the population. So, the table on this slide presents reported prevalences of FAI and FAIS from identified systematic reviews. The data are presented by impingement type and by the presence of labral injury there in the left column in three different populations, the general population, which could be symptomatic or asymptomatic, and athletes. The authors did not consistently report whether athletes were symptomatic or not, but it appears most were asymptomatic. Consistent with the previous report, there is a wide range of reported prevalences of FAI and FAIS. This variability is likely a reflection of the different radiographic criteria and measurement threshold, such as for the alpha angle or crossover sign that were used across the studies to determine FAI morphology. This is one of the issues that makes the true prevalence of FAI difficult to assess. Additionally, systematic reviews in studies generally did not report specific criteria that was used to diagnose FAIS in regards to the triad of symptoms reported previously versus just identifying the morphology. Third, as we've already talked about, FAI morphology may . . . people with this type of morphology may or may not develop symptoms, such as pain or reduced range of motion, and it's unclear why that happens. Again, and important thing to note here is that a large number of asymptomatic individuals in the general population do have radiographic features of FAI morphology and labral tear.

So, the etiology and natural history of FAI and FAIS are also not well understood. FAI is generally considered idiopathic, although there might be a genetic component, as well, and possible associations with high-intensity physical activity during skeletal development, prior surgical procedures, and traumas are also possibilities. The frequency, progression, severity, and mechanisms of symptom development in FAI are poorly understood. It's unclear, again, what may cause the onset of symptoms in some people but not in others, people who have FAI that is. Some recent studies suggest that patient factors, such as mental health status, actually have a stronger association with the presence and severity of patient symptoms than intra-articular findings. Lastly, there continues to be inconsistent evidence linking FAI morphology to the progression or later development of osteoarthritis. In one systematic review, study designs were cross-sectional, making it difficult to assess causality. Other reviews that have included longitudinal studies have reported associations

with osteoarthritis while others have not. These study designs are prone to multiple biases, unfortunately, making inferences challenging.

Female: [inaudible]

Shana Johnson: I would have to ask my colleagues to look that up in the background. I don't think we looked at that in detail, because it wasn't in the scope of the report.

Mia Hagen: So, similar to other areas of orthopedics, when you do preoperative mental health questionnaires, like, a VR12 or something along those lines, you will find that patients that have underlying anxiety, depression, often have lower preoperative patient reported outcome measures, which then also correlate to what their postoperative patient reported outcomes measures would be. That's pretty much consistent across anything in orthopedics, not just FAI, but arthritis, so any total joint surgery, rotator cuff, etc. Which is why, like, a new kind of wave in orthopedics is to really see if there's any way to optimize mental health preoperatively to help with patient outcomes postoperatively. So, that's kind the new push in the literature. So, does that answer your question.

Mika Sinanan: This is a sort of similar followup. If 73% of asymptomatic people have labral tears, that's, like, nearly everybody. So, why is that just not the normal anatomy? Why is that considered an abnormality?

Gregory Brown: Like, low back pain. Do you do you MRIs on somebody with . . . if you do it on 20-year-olds, you're gonna get a certainly percentage than 30-year-olds, than 60-year-olds. So, this is . . . the way I think about it is, like, meniscus in the knee. If you have a tear when you're 20, it's usually acute. It's a problem. It's something that if you don't repair it, there's good longitudinal studies showing that you'll end up with knee arthritis, and the same thing in the hip. If you have a tear when you're 20, it's probably something traumatic, developmental, whatever, whereas you start getting mid-30, 40, or older, it's part of the degenerative and aging process, you know? It's just part of the arthritic process.

Mika Sinanan: So, that's a different question that you're answering. My question is labial injury, if 73% of asymptomatic people have it, why is it even called a pathology? It's the way people are.

Mia Hagen: I would tend to agree that that is a normal thing that we find. Those prevalence studies definitely show a higher prevalence in older patients, though. So, I think the hard thing, and this is something that I find challenging when I counsel patients as well is that we don't fully

understand the relationship that pain has with labral tears and FAI. Similarly, we don't understand the relationship between pain and rotator cuff tears. Right? The incidence of asymptomatic partial thickness rotator cuff tears in someone over the age of 60 is about 70%, as well. Right? We know that from the Yamaguchi studies. So, I think pain is a very poorly understood concept, especially in regard to musculoskeletal conditions. So I don't have a good answer for that, in terms of, like, why are some people hurting and why some people aren't? Why are calling it pathology?

Mika Sinanan: The underlying implication, of course, is if you link it to something that's very common, you will always have an indication for surgery. Right? It's all, everybody has it.

Mia Hagen: Right. And so the, but the, I think what we have found, though, which is why we have been moving to treat these more is that, when you do repair the labrum, you know, restore the bone anatomy to something that is more anatomically normal, then patients get better. Those outcome studies, those longitudinal perspective studies have had convincing evidence about patient improvement. Now, how much of that is placebo versus what you're actually doing? I think you could ask that of, like, a lot of surgical procedures.

Erika Brodt: Moving to our report questions, starting with the contextual questions. Again, these were key questions in the prior report but now are just added for contextual purposes.

So, the first one asks about new information related to the case definition that published subsequent to the 2011 report, and if so, is there evidence of validity and reliability of that case definition from formal diagnostic accuracy and reliability studies. The second part to the contextual questions asks about new validated outcome instruments used to evaluate pain and function in patients with FAIS, and whether or not there is information on clinically-meaningful improvement for those measures.

So, our key questions are pretty standard. They ask what is the evidence of efficacy and effective-, oops. Efficacy and effectiveness, safety, differential efficacy or safety in subpopulations, and cost-effectiveness of hip surgery compared with nonoperative treatment for FAI or FAIS. Consistent with the previous report, we looked at short, intermediate, and longterm outcomes, which are defined for you in key question one.

Regarding inclusion criteria, we included adults and children undergoing primary or initial treatment for FAI, either symptomatic or asymptomatic, although we did not find any studies treating asymptomatic patients. The

intervention, of course, was operative treatment. The comparison was not operative treatment. That was the focus, which can include a variety of things listed there, but not limited to those. So, we did include studies that compared operative interventions, like, arthroscopic versus open or labial repair versus debridement, mainly for completeness and for safety purposes, but we did not do strength of evidence on those outcomes with comparisons. We did do strength of evidence, however, on these primary outcomes, function and pain using validated measures, conversion to a total hip arthroplasty, complications and adverse events, and cost-effectiveness outcomes.

So, for study design, key questions one through three, as usual, we focused on the highest quality evidence. So, those studies with low risk of bias, comparative studies, RCT's primarily. Case series were considered but were not the primary focus on the evaluation. For these questions, given the short length of followup of the included comparative studies, they went out, I think to 24 months is all. We did look for case series with five years or more of followup that reported progression through osteoarthritis or conversion to total hip in order to give a little more information regarding those outcomes.

For safety, key question two, we limited case series to adults to those with at least 40 patients that were designed to look at safety, or comprehensive systematic reviews that evaluated safety, and a full formal economic analysis for key question four. Of note, we placed no limitations on studies evaluating children or adolescents. For publications, as usual, full length studies published in English in peer reviewed journals were considered, and only those published subsequent to the prior report.

So, all comparative studies identified that met inclusion criteria were assessed individually for risk of bias using the criteria that you see here. The top three criteria are specific to randomized control trials. Shortcomings in any one of these areas can introduce bias. Appendix E contains the risk of bias evaluations for all studies, if you are interested. All case series were considered high risk of bias.

So, while the previous slide showed what we do for individual studies, rate their risk of bias, this slide shows what we do across all studies. So, I'm going to be presenting the results in terms of the overall quality or strength of evidence, which is based on AHRQ's recommendations and our application of GRADE, which you all are familiar with, I think. We grade the overall strength of evidence separately for each primary outcome across all the studies that report that outcome, and we use these four criteria. So, risk of bias, which is just one criterion, looks at the extent to

which the majority of included trials that report that outcome protect against bias. Consistency, the degree to which estimates are similar across the studies that report an outcome. Directness, all the outcomes in this study were considered direct. Precision, the level of certainty surrounding the effect estimates. Again, strength of evidence was only done on primary outcomes.

So, to just recap the systematic review process, we identified eligible studies via a formal systematic search of the literature. We assess risk of bias of each individual study, synthesize and analyze the data. Then, we come to a consensus regarding the strength of evidence across comparative studies by primary outcome. The final strength of evidence rating for each primary outcome represents how confident we are that the evidence reflects the true effect. Is our confidence high, moderate, low, or do we have insufficient evidence to draw conclusions. For most outcomes in this report, the evidence was graded low to moderate.

This slide provides just a brief overview of how the strength of evidence criteria are applied and some specifics to this report, just for clarity purposes. So, initially, bodies of evidence comprise primarily of randomized control trials, start out as high strength of evidence. Those consisting mainly of observational studies start out as low. Then, the strength of evidence for a given outcome can be downgraded based on the limitations described previously, one of which is the risk of bias across the studies reporting an outcome. In this report, as has already been talked about by the medical directors, two of the studies were moderately low or good quality studies, the Palmer and Griffin trials, and one was considered moderately high risk of bias. That's Mansell. As you can see, he had a very high rate of cross-over to surgery, 70%, and the loss to followup was higher than acceptable, as well. Of note, he was in a military population. This was done in Madigan. All the studies were unable to blind patients and providers, basically because of the different types of treatment, you just couldn't do it. So, in this report, regarding strength of evidence, the outcomes were most commonly downgraded for imprecision due primarily to small sample sizes, or very wide confidence intervals that included both the negligible effect and appreciable benefit or harm with the intervention. Inconsistency was noted for some outcomes. Where there were single studies, since consistency is unknown, those were downgraded. I'd like to note quickly that since we did have some good RCT data, we did not do strength of evidence on observational studies.

So, our literature search results show that from 1158 citations identified by our search, 79 studies across 81 publications met inclusion criteria and are included in this report.

This slide briefly shows the evidence bases of the prior report and the updated report. So, we most notably, we now have three RCT's comparing operative and nonoperative treatment, whereas the other report had none. An additional RCT comparing arthroscopic treatment for labral tears comparing debridement versus repair was also identified. With the exception of two poor-quality comparative nonrandomized studies, one of which was in adolescents, the remainder of the studies evaluated operative treatment only and consisted of mostly poor quality comparative cohorts and case series. Like the previous report, all studies comparing operative and nonoperative treatment had short-term followup only.

Now to address the contextual questions, I'll try to go through these quickly, if I can. So, we've already talked a bit about the Warwick Agreement and the case definitions. The figure on this slide comes from the Warwick Agreement, and it outlines their suggested pathway for the diagnosis of FAIS. The authors consider FAIS a motion related clinical disorder of the hip, and they emphasize the need, again, for symptoms to be present, that triad of symptoms, clinical signs, and imaging findings that all need to coexist for a diagnosis. Experts consider it a dynamic diagnosis, that is a complex interaction during motion between the acetabulum and the femoral neck. In addition, the document states that further diagnostic testing may be indicated, including diagnostic hip injections, which may be useful in determining whether the pain is really arising from the hip joint or from other structures in the groin or hip region, and where further assessment of hip morphology or associated cartilage and labral lesions is needed, cross-sectional imaging, such as CT or MRI might be indicated. However, the authors do acknowledge that the symptoms and clinical tests talked about here may not be specific for FAIS, and there are no agreed-upon thresholds for imaging. So, the Warwick Agreement acknowledges that there is a paucity of high-quality data on which to base these recommendations. As far as our RCT's, they do, for the most part, pretty much fell in line with this algorithm of diagnosis. Most patients had hip or groin pain or the authors just stated they were symptomatic. All patients had positive imaging signs. Only Mansell specified specific clinical tests that were done.

So, given the criteria recommended in the Warwick Agreement, as a case definition for FAIS, our focus for the second part of this question was on identifying formal validation and reliability studies around these diagnostic criteria. Regarding accuracy, overall, the data was inadequate. No high-quality prospective studies comparing specific criteria to surgery were identified, either in the previous report or subsequent to it. Studies and

those in systematic reviews were retrospective and in highly selected populations. Also, included studies, again, used primarily radiographic criteria for FAI. Regarding symptoms and clinical tests specifically, we identified one retrospective study that explicitly evaluated the validity of a combination of symptoms and clinical tests compared with surgery. Although pain was the most sensitive and specific, the combination of symptoms and clinical tests, while they appear to be sensitive, were not specific. For imaging, systematic reviews report a wide range of sensitivity specificity and predictive values. The variability, again, is likely a reflection of the different criteria and thresholds used for alpha angle crossover sign, those types of things, and different imaging parameters used across the studies. There were no studies of diagnostic injection. For reliability, we found no studies that met inclusion criteria that looked at symptoms and clinical tests, a combination of the two. For imaging, we focused on interrater reliability, which varied, again based on radiographic parameter, lead, or specialty, and patient population across four studies. It was most frequently fair to moderate across parameters, which really doesn't give us a lot of confidence.

Consistent with the previous report, we evaluated . . . so we're moving to question two here about outcome measurements and validated outcome measurements. So, consistent with the previous report, we did evaluate methods used to assess osteoarthritis and included studies. So, the Tonnis identified in the previous report and the Kellgren Lawrence grading system, which is new to this report were used to assess presurgical degree of osteoarthritis, and/or to describe the progression of osteoarthritis during followup. So, two new studies for the Tonnis grading system were identified and showed only slight to fair interrater reliability and fair to moderate intrarater reliability, which is similar to findings from the prior report. Also consistent with the previous report, no psychometric validation studies for the Tonnis clarification in FAI patients were identified. By contrast, a newly identified study reported substantial interobserver reliability for the Kellgren Lawrence scale and construct validity and predictive validity for future total hip replacement were considered good.

Regarding patient and clinical reported outcomes, the prior report identified seven commonly used outcome measures in the FAIS population. Since then, an additional four outcome measures were identified that were used by the RCT's included in this update. They are bolded in the box at the left up there. In general, psychometric properties appear to be good for most of them, as you see here. In particular, construct validity and reliability were adequate for all four. Additional psychometric evaluation has also been done on outcomes included in the

prior report. So, in total, we have eight measures that have undergone some kind of psychometric evaluation in our population of interest.

So, for the four newly identified outcome measures, we did identify minimally clinically important differences in patients with hip pain and/or hip related procedures. In addition, we found evidence of a patient acceptable symptomatic state, or PASS, in one prospective case series. As you can see, some of the outcomes listed here have multiple MCIDs associated with them. That's because MCIDs can vary, depending on the patient population they are validated in and the methods used to determine them. Only one of the included RCT's reported the proportion of patients that met an MCID or PASS, and that was Palmer, as described previously.

Getting to our research questions, this slide provides a brief overview of the evidence base by comparison and key question. Of the 79 studies included, only eight compared operative with nonoperative care and included three RCT's, two cohorts, and three cost utility analyses. Again, consistent with the 2011 Health Technology Assessment, this comparison was the focus of our report. The remaining studies compared or evaluated various operative approaches for FAIS. Of these studies a total of 14 were in adolescent populations and included one observational cohort comparing arthroscopy versus conservative care. The remainder were case series, 11 of arthroscopy and 2 of open hip surgery.

Getting to our key question one, operative versus nonoperative comparison, which again is the focus. I keep belaboring that. This slide is just meant to give you a brief overview of the patient characteristics in the three included RCT's to give you a sense of how similar or different they might be. So, the mean age was similar across all of them with patients being fairly young in their early to mid 30's. To me, that's young. Compared with the other two trials, Palmer enrolled fewer males. Patients had symptoms of FAIS for over two years in two of the trials. Palmer did not report symptom duration in that population. Cam impingement was the most common morphology addressed in two trials. Mansell did not report the type of FAI, but it appears from the surgical data that all three types were addressed. All trials excluded patients with preexisting OA and prior surgery. Additionally, Mansell and Palmer excluded patients who received a formal course of physical therapy within the previous six to twelve months while Griffin did not. It was not clear how many patients in Griffin might have just got done with a failed PT of course.

So, this gives an overview of the treatment characteristics, as well. Griffin and Palmer, again, they provided details of the surgical procedures

performed during arthroscopy. Femoroplasty was the most common type of osteoplasty performed in over two-thirds of the patients in those studies, which makes sense, because cam type impingement was the most common. Additionally, 90% or more of patients had procedures to address labral injury, as has already been stated previously. They underwent repair, debridement, or even thermal shrinkage was mentioned. Mansell, again, did not provide any details. He just stated that patients received one or more of acetabuloplasty, femoroplasty, labral repair, or debridement. Regarding postoperative care, all patients were described to have received physical therapy or rehabilitation postoperatively, per the provider's routine care. However, specifics were not well described by any trial. Regarding individualized supervised PT, I know there's a lot of stuff up there, but as you can see if you read through it, the specific therapy components and the number and frequency of treatment sessions vary quite a bit across the trials, speaking again to no standardized approach to this type of physiotherapy treatment. Sessions range from six to twelve over one and a half to six months. It's really unclear what the impact of this might be on the results. I would also like to mention that regarding concomitant care, with the exception of intraarticular steroid injections, which were specified by Palmer as being excluded. They specifically told patients they could not have. There were no other restrictions placed on additional treatments patients could seek during followup. There is not really a good indication of what those might have been, and therefore, how that may have impacted results.

Getting to our outcomes, for the iHOTT-33, our first functional outcome, this was reported by all three RCT's. At six to eight months, we can see a small improvement favoring arthroscopy, but again, the difference is likely not clinically important. It's pretty small on a scale of 0 to 100. It's also driven by Palmer, as you can see there. Now, we didn't show it on this slide, but when we ran the sensitivity analysis removing Mansell, the poorer quality trial, the point estimate is actually attenuated slightly. The difference is no longer statistically significant. So, it actually drops to 1.58 with a confidence interval of -0.35 to 3.5. The strength of evidence is moderate for that outcome. At 12 months, we see no clear differences between groups across two trials. Again, when we look at the better quality trial, in this case Griffin, we do see a statistical significance favoring arthroscopy, but the confidence interval was wide. Again, the clinical relevance is unclear. Strength of evidence was insufficient at 24 months with only the one trial by Mansell. He found no difference.

Regarding the HOS-ADL subscale at six to eight months, there was no difference between groups when considering Mansell and Palmer together. Looking at Palmer separately, again considered the better quality trial,

there was statistical improvement favoring arthroscopy versus PT. The difference may be clinically important. Again, the MCID reported in this trial was nine, and we have found other MCIDs, I think ten was one. So, again, it kind of pulls into question the clinical significance. At 12 to 24 months, there was no difference between groups at either time point. Again, this is Mansell. Insufficient strength of evidence for him.

For the HOS-Sport subscale at six to eight months, we see improvement again with arthroscopy versus physical therapy. The difference may be clinically important, again, driven by Palmer, the one trial. Strength of evidence was moderate at six to eight months and again at 12 to 24 months, we only have Mansell. He is the one that had the longest followup. Again, insufficient, no difference between groups. Palmer also reported a variety of other functional outcomes and found that arthroscopy was superior over PT at eight months, but the clinical relevance of those is unclear. They are not included here, but you can find them in the full report on table 20 if you're interested.

So, pain was reported less often by the trials. There was greater improvement in pain, based on the Copenhagen Hip and Groin Outcome Score, the HAGOS, in patients who received arthroscopy versus physical therapy at eight months. In one RCT, Palmer, the difference may be clinically important, but the confidence interval, again, is wide. The same trial found fewer arthroscopy patients had pain on clinical tests, which included hip flexion, hip abduction, and the Faber test, but there were no differences on other hip assessments. The clinical relevance, again, of differences is unclear. The strength of evidence is low for both of these pain outcomes. Again, our friend, Mansell, evidence was insufficient regarding prescription opiate pain medication use at 24 months. There was no difference between groups on any metric analyzed. As you can see, the confidence intervals are extremely wide.

So, two of the RCT's reported whether patients underwent subsequent total hip arthroplasty. A total of two patients, one in each trial, required conversion to total hip, both of which had received arthroscopy, and followup periods were 12 and 24 months. The difference between groups was not statistically significant. Followup may not have been long enough to adequately capture this outcome. In addition, sample sizes were relatively small. Strength of evidence was low for this outcome.

So, this slide gives a brief overview of all the secondary outcomes reported by the RCT's. Again, strength of evidence was not done for these. So, all three trials reported different measures evaluating patient quality of life, mental health status at various timepoints. Additionally, range of motion

and return to work was reported by one trial each. The only statistically significant differences seen were for the hospital anxiety and depression scale depression score, the HADS-D, and range of motion, specifically flexion, in one trial, again Palmer, which show greater improvement with arthroscopy at eight months. One small RCT found no statistical difference between groups in the risk of progression to osteoarthritis over 24 months. Again, this is Mansell, though the frequency was somewhat higher following arthroscopy versus PT. Results were similar. I didn't mention this previously, but Mansell, because of the high cross-over, along with intention to treat analysis, he also did a per protocol, or as treated analysis, and really all the outcomes were more or less identical. So, it didn't change anything.

This slide shows all the data that we have reported by the two poor quality cohort studies that evaluated the effectiveness of operative versus nonoperative care. Again, we did not do strength of evidence on these. One study was in adults, and one was in adolescent athletes. In both cases, they underwent a nonoperative treatment protocol prior to being offered arthroscopic hip surgery if they failed to improve. The studies did differ. The adults had a more passive conservative care approach. The children had a formal physical therapy program. Regardless, there were no significant differences between groups on any measure.

Now, we turn to the operative versus operative part of key question one. Again, this was not the focus of our report. We did not do strength of evidence on it. This slide shows the data from on small RCT that we identified, which was at moderately low risk of bias. Both groups showed improvement postsurgery. Patients who received labral repair versus labral debridement reported significantly better function and a greater proportion of patients considered themselves to have normal function at a mean followup of 32 months. When comparing change scores from baseline to followup, the two treatment groups actually appear a bit more similar. No other outcomes were reported by this trial. The results of this trial should be interpreted with some caution given the small sample size and apparent substantial imprecision, as you can see from the wide ranges there.

So, we identified 12 observational cohort studies that provide data, again, on the effectiveness of one surgical approach versus another, predominantly arthroscopy versus open hip dislocation, and labral repair versus debridement. Sample sizes, mean age, and proportion of females varied widely across the studies. No study provided information regarding symptom duration or if athletes were included in their population. All patients were symptomatic with radiographic evidence of FAI morphology,

primarily mixed type. Other diagnostic criteria was reported less consistently. These studies were primarily poor quality due to the lack of assessor blinding, failure to control for confounding, and high attrition rate.

Across these studies and across the functional and pain outcome measures they reported, the results varied, but in general, function and pain did improve with surgery. Results were generally comparable between the operative groups. If there was a difference, arthroscopy tended to be favored over open, and labral repair over debridement. Some differences may be clinically meaningful.

So, half of the cohort studies reported whether patients required a total hip replacement during the followup period. There were no statistically significant differences between operative approach, and this includes various different operative approaches. However, some differences may be clinically meaningful regardless of operative approach. The frequency ranged from 0 to 13% over these studies, and the longest followup was 12 years, I believe. Sample sizes were small. Again, followup may not have been long enough in the majority of studies to adequately capture this outcome.

We're still talking about effectiveness, but now we're talking about case series. The next two slides will present overviews of data from the case series. Please see the report appendix G for details if you're really interested in all the nitty gritty details of these studies. The first slide is going to present data on adults, and the second on adolescents. Due to the relatively short followup periods, again, I think I stated this before a couple times maybe, in the RCT's, we included studies with at least five years of followup or more that reported progress to OA or the need for a total hip.

So, across the 13 case series that met inclusion criteria, the frequency of conversion to total hip ranged from 2 to 34% of patients across nine studies, and 3 to 17% of hips across four studies over followup periods ranging from 5 to 11 years. In addition, we identified two large systematic reviews of case series, which reported frequencies of approximately 6.3% in about over 7200 patients, and 6.5% in almost 2000 hips.

For progression to OA, we found three small case series, one of arthroscopic treatment, and two of open surgery. The frequency in these studies ranged from 8 to 12% over 84 to 132 months. [7 to 11 years]

So, these are the case series in pediatrics or adolescents. Given that none of that RCT's that we had, and only the one cohort at high risk of bias reported on kids. We decided to go ahead and give an overview of all the outcomes they reported, just so you get a sense of how kids do with this. Again, strength of evidence was not reported for any of these outcomes. We identified a total of 12 case series of varying size that evaluated adolescent patients, about age 14 to just under 18, who had undergone surgery for FAIS. Arthroscopy was the surgery in 10 and open in 2, as I said before. A statistically significant improvement from baseline to followup was reported for both function and pain across various measures. The proportion of adolescent athletes that returned to sport was high across the studies at 86% to 100% over followup periods up to 40 months. No cases of conversion to total hip over 40 months in one small case series.

So, now, we're going to talk about safety. OK. So, this first slide is the only slide we have with comparative data for safety. This is for the RCT's. Our focus was on serious treatment related and treatment related adverse events. These events were fairly infrequent and were more common with arthroscopy. There were a total of five serious treatment related adverse events versus none with physical therapy across two trials, Griffin and Mansell. All five of them were reported in the trial by Griffin and included two hospital admissions, two superficial wound infections requiring oral antibiotics, and one hip joint infection requiring further surgery and ultimately a total hip replacement. Additionally, Griffin also reported treatment related deaths, which did not occur in either group, as well as other potentially treatment related adverse events, which were significantly more frequent following arthroscopy. However, the confidence interval was wide, as you can see, 1.1 to 66.8. Sample sizes and followup may have precluded identification of rare events. We graded the strength of evidence low for these outcomes. Griffin, again, further reported various other complications, unclear the relation to treatment in some instances and in others some are to be expected. There are no statistical differences between groups. OK. So, this slide gives an overview of adverse events associated solely with operative treatment, and this is in adults, and it's across several different types of study designs that we identified. Systematic reviews of case series is the first column, the included RCT's, all of which evaluated arthroscopic surgery. The comparative nonrandomized cohorts and case series, both of which were primarily arthroscopic surgery. So, followup varied widely across these studies from one and a half months to 120 months. The comparative cohorts were essentially treated as case series for these purposes, but if there are any differences between the frequency of adverse events between the type of operative approach, we called this out in the report, and I will call it out here as well.

So, for adults, the case series summarized here in the right hand column were limited to those with at least 300 patients. We had a lot of very small case series. For results from case series, if you want all of them, you can see section 4.34 in the full report, or Appendix G. So, overall, the rate of adverse events following operative treatment was low with the highest frequency seen for revision surgery. There were five patients in one RCT, Mansell, that went on to have revision surgery. There were no further details about exactly the issue surrounding those. Up to 12% of patients in the open hip dislocation arm of one of the cohort studies had to have revision surgery, and when we excluded any open surgery and looked only at arthroscopy in those studies, the range dropped slightly to 10%. For case series, the range was 1.2 to 6.5, and that was for the largest case series with the longest followup, 6.5%. Nerve injury was the other outcome that had kind of a higher frequency. All of these were following arthroscopy. It was in up to 9% of patients in the included cohorts, and up to 19% in one case series. The authors did classify all of those as minor. All of these nerve injury events were transient and resolved on their own. We considered the strength of evidence low for all of these.

Finishing up with the adults, again, the frequency of infection or thromboembolic events following operative treatment was generally low. Superficial infection was the most common adverse event reported and range from 0 to 6%. That 6% was following arthroscopy across all study types, but it was only 1% or less across just case series or SRs of case series. Only 2 of the 10 superficial infections reported by the RCT's were considered serious, because they required oral antibiotics, but they did improve after treatment. None of the infections reported by the cohorts were labeled as serious. For the remaining adverse events, frequencies across them range from 0 to 3%. The 3% seen for DVT corresponds to 1 patient in a small cohort study of 40 who received arthroscopy. Again, strength of evidence was low.

This slide is similar to the previous slides we just reviewed for adults, but these adverse events are in adolescents and are confined to case series or systematic reviews of case series. So, we had no other data. The one cohort study that we included for operative versus nonoperative did not report adverse events. Events associated with operative treatment in adolescents were again relatively low with the highest frequency seen, again, for revision surgery 0 to 6% following arthroscopy, and 0 to 14% following open surgery. Nerve injury, up to 8.3% in one case series. Also, additional surgery, other than revision, ranged from 2 to 11%; however, this was across two very small case series. Importantly, there were no adverse events specific to adolescents, that is the skeletally immature

population, such as physeal arrest, growth disturbance, acute iatrogenic slipped capital femoral epiphysis, or instability, as well as no cases of avascular necrosis, femoral fracture, or nonunion. Again, strength of evidence was low.

For key question three, differential efficacy and safety, two of the included RCT's, Griffin and Palmer, who compared arthroscopy with physical therapy did do formal test for interaction, in order to evaluate subgroups that might have a differential treatment effect. Age was found to modify the treatment effect in one trial, Palmer, but not in the other. Palmer found that function may be greater and in favor of arthroscopy compared with physical therapy for younger patients with the effect decreasing with increasing age. And of note, the Palmer trial evaluated age as a continuous outcome, whereas Griffin dichotomized age by less than 49 to greater than 40. So, the Palmer trial might have had more power to detect an effect in that case than Griffin, but again, the strength of evidence here is insufficient to determine if age really impacts treatment. As you can see, there was no interaction scene for the other variables listed there.

So, regarding cost-effectiveness, in total, we identified three cost utility analyses; however, only one, Griffin shown here, which is the same trial included for the results, used data from a head-to-head RCT comparing arthroscopy with nonoperative care, as I've stated previously, personalized hip therapy or physiotherapy. It's also the only cost utility analysis that used validated outcome measures, the EQ5D and the SF12. Of the three, this one was considered to be the most well done and the highest quality. It was considered to be moderate quality based on the QHES and consideration of other factors described in the appendix and methods. It was conducted in the United States and funded by the Health Technology Assessment program of the National Institute of Health Research. So, the findings from this analysis showed that PT dominated surgery over a 12 month time period from a societal perspective. Surgery was found to be both costlier and less effective than physical therapy. In sensitivity analyses, results from the base case analysis remained, for the most part, robust, and at a willingness to pay threshold of just over \$67,000, the probability that surgery became cost-effective was only 8%. So, the authors concluded that personalized hip therapy was more cost-effective than arthroscopy at 12 months. However, cross-over to surgery increases the cost of physical therapy and makes surgery increasingly cost-effective. Longer term data is needed around that. So, the limitations of this study were the short time horizon, only 12 months, which is inadequate to evaluate longer term outcomes, as well as the impact of any additional interventions that might have been needed. The methods for determining indirect costs, such as lost wages and how cross-over was or was not

modeled were not clear. The generalizability of the UK healthcare system to our system here in the United States is unclear.

So, this cost-effectiveness cost utility analysis by Shearer is one of two U.S. based analysis that we identified that met inclusion criteria. Some assumptions and methodological components from this analysis were carried over into the more recent cost utility analysis by Mather, which will be described next. This study was considered poor quality. The population and clinical data are primarily from case series, describing outcomes following arthroscopy for FAIS. The comparator was observation only. Again, the population and clinical data are primarily from case series describing outcomes. So, the comparator was observation only. It's unclear exactly what that means, or if any treatments may have been provided during that time. The source of funding was not recorded. The authors found that compared with observation, arthroscopy is cost-effective in patients with FAIS who do not have osteoarthritis. The authors modeled outcomes over a lifetime, and the perspective was unclear, but likely payer or hospital. They found that estimates may be robust in their sensitivity analyses. So, although the data are limited, the models suggest that arthroscopy in FAIS patients without osteoarthritis may have a favorable ICER versus other interventions. Uncertainty remains regarding quality of life, duration of benefits, and the effect on subsequent total hip arthroplasty. There are many limitations to this study. The quality of data from modeling came again from case series, and authors acknowledged the limitations related to poor quality of available data. The rate of osteoarthritis is unknown. The impact of age, activity level, degree of deformity were not incorporated into the model and accounted for. Lack of specificity of treatments received in the nonoperative group is a problem. Estimations of utility or disutility was based on modeling of arthroscopy patients modified Harris hip score before and after arthroscopy, and the method of determining utilities was not validated.

So, the second of the two U.S. based cost utility analyses, Mather, again, used a lot of the same assumptions from Shearer previously. The modeled patient population had 'noncontroversial' indications for surgery. Again, it's unclear what that meant exactly other than the limited information provided here. The had Tonnis grade 0 or 1 osteoarthritis and only mild hip dysplasia was allowed. All modeled patients had labral tears and had received either acetabuloplasty or femoroplasty. Arthroscopy was compared to a variety of nonoperative therapies, as you can see there. Again, most of the clinical data came from case series or retrospective patient surveys, which are subject to recall bias and expert opinion. This study was funded by industry, as you can see there, which brings into question if perhaps the other study might have been as well, since it used

much of the same assumptions. So, the findings, based on the Markov model arthroscopy was shown to dominate nonoperative treatment over ten years from a societal perspective. Again, based on their sensitivity analyses, all variables were robust with time. The authors concluded that arthroscopy greatly reduced the economic cost of FAI while contributing to improved quality of life in patients with 6 to 12 weeks of nonoperative treatment before surgery. Again, this study has multiple limitations. The clinical data came from case series, patient surveys, and expert opinion. Nonoperative patient characteristics and outcomes were not defined, and data from patient recall preop status versus directly from those receiving nonoperative treatment is again a problem. Utility methods were all unvalidated. Also, patient selection was from a high volume hip arthroscopy center and generalizability again is unclear.

Kevin Walsh: And it was also an industry funded study.

Erika Brodt: Yes. So, to get to the summary. So, for contextual question one, case definition, in summary, the 2011 report found insufficient evidence of a consistent case definition for FAIS. We used inclusion/exclusion criteria from the included studies previously in the absence of another case definition. Although work has been done, since the previous report to further define the clinical presentation of FAIS, no new prospective evidence was identified. There remains a paucity of high quality prospective and comparative studies on which to base an FAIS diagnosis and treatment recommendations, and this is acknowledged by both the 2016 Warwick Agreement and the 2019 Best Practice Guideline by Lynch. Additionally, signs and symptoms described by the Warwick Agreement are not necessarily specific to FAIS and may be present in other hip conditions. Further, there are no agreed upon radiographic thresholds. So, we conclude the previous report's conclusions are still valid.

Regarding diagnostic accuracy and reliability, the prior report found insufficient evidence for the diagnosis of FAIS by clinical examination and for the reliability and validity of imaging parameters. For this report, no high quality prospective data on the accuracy of diagnostic criteria described in the Warwick Agreement compared with surgical findings were identified. The evidence base cited in the studies is poor, and none of the criteria described are pathognomonic for FAI or FAIS. For reliability, there continues to be a lot of variation across most imaging parameters, and no studies meeting inclusion criteria were identified that showed reliability of symptoms and clinical tests. So, the previous report conclusions are still valid.

Contextual question two, which is talking about the outcome measures, again consistent with the previous report. There were no validation studies for the Tonnis classification of osteoarthritis in FAI patients identified for this update. Two new studies reported only slight to fair interrater liability, and fair to moderate intrarater reliability. This update report did identify evidence on an additional OA grading system used by the included studies, the Kellgren Lawrence, which showed good construct validity, predictive validity, and substantial interobserver reliability. Regarding patient and clinician reported outcomes, the prior report identified seven measures. We found an additional four, construct validity and reliability were adequate for all four, and other psychometric measures and testing appeared to be adequate. In total, we had eight outcome measures that look at this population of interest and have been validated. In addition, we found updated minimal clinically-important differences in patients with hip pain and/or hip related procedures for those outcomes identified, as well as a PASS, which is the patient acceptable symptom state.

So, before getting into the other summary, this is a general evidence summary, just to reiterate even though I probably don't need to do it again, that comparative studies of operative versus nonoperative treatment were really our focus. The prior report had the one poor quality cohort. We found three new RCT's; however, the comparative impact of arthroscopy versus nonoperative care, in our opinion, is challenging to assess, given the differences in methods, populations, comparators, and treatments used across the studies. We still have no longer term data, nothing that goes out longer than really two years, definitely not more than five. Systematic reviews of arthroscopy management were primarily poor quality studies, case series, and retrospective cohorts. Surgical studies were primarily retrospective.

Regarding efficacy for the operative versus nonoperative care, across the three RCT's, improvement was seen at six to eight months for all outcomes, which favored arthroscopy; however, the HOS-Sport difference is likely the only that's clinically important. I'll mention that again for Mansell when you did remove him from the six to eight month metaanalyses results of the iHOT, the difference became then not significant anymore. More arthroscopy versus PT patients achieved a minimally clinically important difference, and achieved a PASS on the HOS-ADL in the Palmer study. The strength of evidence for these were low to moderate, as you can see there. When we get out to 12 and 24 months, there were no clear differences between any groups on any measure. Again, if we remove Mansell, the Palmer trial is significant at 12 months for the HOS-ADL.

Mia Hagen: I wonder if I can clarify one point on here. So, these followup periods are post-randomization, not postoperative. So, both these trials were, I think, with the NHS. So, patient time to surgery was on average four months in one and three months in another. So, the followup on the six to eight months is postoperative followup is like two to three months. So, just keep that in mind when interpreting the data here.

Erika Brodt: OK. For pain, one RCT found improvement with arthroscopy versus physical therapy at eight months, which might be clinically important, but again, the confidence interval is wide. There was inconsistency regarding pain improvement on other assessments. Only two RCT's reported conversion to total hip arthroscopy, occurred in two patients versus no patient who had physical therapy up to 24 months followups. Sample size and short followup, again, may impact the ability to adequately capture this event. Strength of evidence for that was low, and no studies reported progression to osteoarthritis, none of the RCT's.

For effectiveness, our findings were generally consistent with those of the previous report. We did identify two cohorts, one in adults and one in adolescent published since the prior report that compared arthroscopy with conservative care. There were no differences between groups in function or return to sport. These studies were small and prone to multiple biases. Across 12 mostly poor quality cohort studies comparing various surgical approaches to FAIS, in general function and pain improved with surgery and results were comparable between surgical groups. Again, when there was a difference, it tended to favor arthroscopy over open surgery and labral repair over debridement. Half of the studies reported conversion to total hip arthroscopy, which ranged from 0 to 13%, up to 11 years of followup. Only three small case series with at least five years of followup were identified that reported progression to osteoarthritis, which was seen in 8 to 12% of patients. Like the prior report, we found no evidence of effectiveness over the intermediate or longterm, and there is still insufficient data to test the hypothesis that FAI surgery prevents or delays hip osteoarthritis or the need for total hip arthroscopy.

So, regarding safety, the data was insufficient in the prior report to draw conclusions. For this update, we have low strength of evidence regarding the safety of arthroscopy. The frequency of most serious surgical complications in both adults and adolescents appears to be low. The most common complications in adults were transient nerve injury and revision surgery. Importantly, there were no cases of adverse events specific to skeletally immature populations, such as physeal arrest or growth disturbance. When compared with physical therapy across two RCT's, serious and nonserious treatment related adverse events were infrequent

but did occur more often following arthroscopy, and there were no treatment related deaths.

Key question three, we have insufficient evidence to draw conclusions regarding whether any of these factors might modify the treatment effect. For cost-effectiveness, conclusions regarding the cost-effectiveness of hip arthroscopy compared with nonoperative care were inconsistent across the three cost-effectiveness analyses. Only the one based in the UK had RCT data from a head-to-head comparison. Personalized PT was found to be more effective and less costly than arthroscopy at one year. The short-term time horizon precluded the evaluation of osteoarthritis development or conversion to total hip arthroscopy. Two poor quality cost utility analyses from the U.S. were also identified. They both found arthroscopy alternatively to be more cost-effective than nonoperative care from a societal perspective over ten years in one and more cost-effective than observation, again not well defined from a hospital cost perspective for a lifetime. In those two studies, the primary data sources were case series, expert opinion, and retrospective surveys of arthroscopy patients, and both used unvalidated methods for determining utility.

This is a slide that just briefly talks about some of the evidence gaps and remaining questions that we feel still exist. The characterization and specification of FAIS as a distinct pathologic entity with discrete diagnostic criteria still remains unclear, in our opinion. Benefits of arthroscopy versus nonoperative care also remain unclear. There was inconsistency across the trials. Some effect sizes were small and of unclear clinical importance. The question of whether improvement with surgery is due to the surgery or to whatever the patient is getting postsurgery, the rehabilitation postsurgical activity modification, or even placebo effect, I think, as was talked about previously is still unclear and is a question that we have. Different approaches to nonoperative care are reported in the literature and were reported across our RCT's. Again, this lack of standardization makes comparison difficult. So, talking about the labral repair issue, again, the vast majority, over 90% of patients, who are having surgery in these studies had labral tears and had procedures to fix those labral tears. So, the question regarding whether labral or cartilage procedures without changes in bone morphology might result in a similar relief. The extent to which labral pathology with FAI is due to bone morphology versus another cause is unclear. Does changing the bone really prevent future tears in well done quality comparative studies? Only short-term comparative evidence was available. We have no longterm evidence. So, for operative versus nonoperative, again, the impact on progression to OA, we feel, is unclear from the evidence, and the impact on total hip arthroscopy is unclear. Natural history is also unclear. Questions?

- Gregory Brown: Thank you. I have not done a very good job of managing our time today. I apologize. I don't think we have time for a break. If you need a break to go to the restroom or something, or get something, a snack or something to drink, please do so. I would say we just go into our questions. We ask as we go along, if nobody has any real questions, then we can do our . . . this is our straw vote.
- Sheila Rege: I like doing the straw vote right off.
- Gregory Brown: Yeah? OK. Are we good with that? OK. So, I got the wrong order. I guess safety was first. So, first of all, what's our comparator? Should we do physical therapy? Not open versus arthroscopic? So, our comparator is that. So, the first thing on our tool is safety. Safety of arthroscopy or hip surgery versus physical therapy.
- Sheila Rege: So, when you say less, what's . . .
- Gregory Brown: So, it is less . . . surgery is less safe than therapy.
- Josh Morse: OK. I'm gonna count the lesses first. I see one . . .
- Sheila Rege: Surgery is less safe than . . .
- Josh Morse: . . . two, three, four five, six, seven lesses. Equivalent I see one equivalent, and I am going to guess that leaves one, two, three unproven? Two unproven. That adds up to ten.
- Gregory Brown: So, I have a question for the group. What are the complications of therapy?
- Laurie Mischley: If you believe it works, which I . . .
- Mika Sinanan: Or accidents on the way to and from.
- Gregory Brown: OK. Just asking. How can surgery not be less risky, I guess. OK. So, the second one is efficacy. Again, physical therapy versus . . . so efficacy . . .
- Sheila Rege: Is surgery better or physical therapy better?
- Gregory Brown: . . . surgery is the treatment. So, more in some would mean surgery is better in some patients.

- Josh Morse: Count unprovens first. I see one, two, three, four, five, six, seven unprovens. One, two more in some, and one equivalent. That adds up to ten.
- Gregory Brown: Cost, so if we're saying surgery is more costly, then it would be more in all or some. If it's equivalent, or they're the same, then it's equivalent. If therapy is more costly, then it would be therapy is . . . or surgery is less than physical therapy. Does that make sense. So, we're doing cost-effectiveness compared to physical therapy. Right?
- Mika Sinanan: Surgery compared to physical therapy.
- Gregory Brown: Surgery compared to physical therapy. So . . .
- Sheila Rege: So, if I say more in some, that means surgery is more costly?
- Josh Morse: Cost effective or . . .
- Gregory Brown: More, well, OK. I said costly.
- Sheila Rege: Costly or cost-effective.
- Gregory Brown: Cost effective. So, cost effective.
- Janna Friedly: I think cost-effective makes more sense.
- Sheila Rege: So, surgery is more cost-effective.
- Josh Morse: OK. I will count unprovens first one, two, three, four, five unprovens. Thank you. Then, the last one, two, three, four less, and one more in some.
- Gregory Brown: So, with our straw vote, we have surgery is less safe. There's no proven effectiveness with seven, and five unproven on cost-effectiveness. So, based on that vote, we have a dangerous ineffective, unproven treatment.
- Mika Sinanan: That may help some people.
- Gregory Brown: Anybody . . .
- Mika Sinanan: A hard ad campaign.
- Gregory Brown: . . . anybody want to argue against what the votes are?

Mika Sinanan: So, I would ask Mia, what you said sounds different than what the evidence would support. So, can you give us some perspective?

Mia Hagen: Yeah. I think one thing that we struggle in this topic . . . there's a lot of things. So, regarding the randomized control trials, which there are more recently, because this has been kind of a hot topic, as there are certain states, like Washington, that don't cover it. The issue with the randomized control trials is, one of the ones, the Mansell one, in particular, is challenging to interpret due to the cross-over rate. So, if 70% of the people in the nonoperative group ended up having surgery, and you have an intention to treat analysis, the fact that they found no difference between groups at two years should be expected if . . . because they're essentially getting the same treatment. The other challenge with that RCT was the high loss to followup rate, which makes it pretty flawed. So, then you have the other two RCT's, which I think actually are good quality RCT's, and they have been published in the last two years. Looking at the way that they were aggregated on the metaanalysis, it's a little bit confusing, because it's not actually assessing their postoperative recovery. So, standard recovery after hip arthroscopy is six months to a year. Prior to six months, there is still a fair amount of inflammation associated with the surgery and atrophy associated with the surgery, similar to, like, if you said what's our ACL return to function at three months. Right? Return to sport. That would be 0%. Right? So, the challenge on interpreting the way it was aggregated there is that you're kind of still, like, assessing some of these people. At six months, for example, that wasn't the primary outcome of the one RCT was the 12-month post randomization, because then most patients, they figure would be at least six months postop. So, comparing that six month to the other eight month followup is a little bit unfair, because it's kinda like someone is still recovering from surgery. I think in clinical practice the reason why I do hip preservation and hip arthroscopy is because I see people get a lot better. That's, like, obviously biased, because I'm the surgeon, but I wouldn't do it if I felt like people weren't improving. That is supported by a lot . . . mostly a perspective cohort data longitudinal studies of a lot of it just single surgeon and just seeing the . . . a number of patients that have reached MCID through that is pretty tremendous when you look at that body of literature. So, it's hard in any surgical field to have a well-run RCT, because you can't blind surgery. So, most of our data in surgery comes from prospective studies where we collect cohort data. So, again, the way that it's presented makes it a little bit unfair to the actual body of literature that exists on this topic. So, I read the report. I saw all the things that were presented. I think I disagree in the way that it was presented, mostly because it is sort of . . . it doesn't demonstrate all of the numbers of improvements. Like, if I threw up the preoperative HOS scores on all my patients and the postoperative HOS scores, you would see the amount of

improvement. If I did the same with people that are just getting physical therapy because they don't want surgery, it would be less of an improvement. So, I think that's challenging. The other thing I would like to say is that in the state of Washington, there are the three main insurers that follow these guidelines, and it is a bit frustrating for those patients, because they either change insurance during open enrollment, or they pay out of pocket for surgery. So, they are still getting the surgery, though. So, that's just another thing to consider.

Janna Friedly: You had talked about labral tears and the relationship between the labral tears and the bone morphology changes. Their coverage policy currently will cover labral tear repairs. Right? What do you do when you have somebody who has a labral tear and this morphology that's younger than you think, you believe that there is a relationship between those two. One of the procedures is covered and one isn't. Practically surgery, do surgeons go in and repair the labrum and not take off some of the bone?

Mia Hagen: I think it is almost malpractice to just do one and not the other. So, I don't offer them surgery, because I think that they're just going to get a re-tear, which is what a lot of the data shows when you do isolated. You know, there is a trial that's underway looking at that question, an RCT out of Canada that is still in the process of collecting patients. So, it hasn't published any data yet, but I think it will be helpful, but I have a strong sense that the bone impingement really does contribute. When you look at it intraoperatively and you see the area in flexion and adduction that pinches that portion of the labral tear, it really looks like a very clear, like, A and then B. So . . .

Janna Friedly: So, you would not do surgery at all?

Mia Hagen: I will tell them that I don't think it will help them to just do that. So, I prefer not to, because I don't want to surgeries that I think don't have efficacy for the patient population.

Janna Friedly: And what percentage of patients do you think with FAI have labral tears versus ones with just the bone morphology changes and no labral tears that are . . .

Mia Hagen: I think it depends on . . .

Janna Friedly: . . . symptomatic.

Mia Hagen: . . . their age. So, FAI obviously is a morphology that people are born with, and there is some amount of development that goes into it, as well, but if you have a hip that has had that morphology for ten years longer than

another hip, you're probably more likely to have a labral tear, but it's also multifactorial in that it's activity dependent, as well. I think that patients do more sports where they are bringing their hip up into those positions, the flexion, that they are more likely to be developing them. So, I don't know the exact percentage. I'm sure there are studies showing that, looking at these two groups with the same x-rays, what was the percentage of labral tear versus not, but I would guess it is dependent on age and activity.

Janna Friedly: Do you think that your . . . the way that you practice is similar to most orthopedic surgeons in terms . . .

Mia Hagen: I would say what . . .

Janna Friedly: . . . of the labral . . .

Mia Hagen: . . . I do is consistent . . .

Janna Friedly: . . . tears?

Mia Hagen: . . . yeah, with, I mean, I'm a member of the International Cyberhip Arthroscopy. When we go to the meetings, it's pretty consistent who high volume hip preservation surgeons are practicing. I think what is a little bit dangerous about this technology is that if you don't do . . . hip arthroscopy is a technically challenging procedure and you need to do it a lot to be good at it, which I think is not the same with shoulder arthroscopy and knee arthroscopy. There are studies showing that depending on the number of hip scopes you've done, your patient outcomes are different. So, you kind of have to be a surgeon who is doing a lot in order to be doing this procedure correctly. I get a lot of referrals from around the area of patients that have surgery that, to me, looks like it was not correctly done. Then, we end up doing revision and find all these problems. Right? So, I think that is the challenge. Right? It needs to be done in a center where the person doing it does a lot of it and knows what they're doing and understands the true indications, such as, I just did a market scan study looking at the number, just age and conversion to total hip after hip arthroscopy across the country on a commercial payer basis, it's astonishing how directly it correlates with age to the point where I do think that patients over the age of 60, or if there are any signs of arthritis, really should not be getting this procedure, because it's not going to treat their arthritis. I think that's a misconception from earlier on in hip arthroscopy when people thought it could be used as, like, an intermediate stage for a way to debride cartilage, etc. Similar to in the knee, our understanding of ability to preserve the knee by doing cleanup surgery for degenerative

meniscus tears with existing osteoarthritis. Right? That's been shown to not be helpful. So, I think that is a very similar analogy in hip preservation and why you need to have very strict indications for surgery. That does help optimize your outcomes. So, another problem with a lot of the existing data, especially the older studies, is that the groups of patients that they were studying often had a fair amount of arthritis. So, that obviously biases the results.

Seth Schwartz: One of the things I'm struggling with a little bit is determining exactly who has this condition. It seems like the . . . you described some of the physical findings and some of the complaints that people have. Then, you obviously have to correlate that with the radiographic findings, but I look at what, the Tonnis grading system. I look at the interrater reliability, which is, like, 0.17, which is terrible. Even the best . . . the intrarater reliability is below 0.4, which is pretty poor. So, even the same person isn't calling these radiographs the same the majority of the time, and when two different people are looking at it, the majority of them are having different findings. So, for a syndrome that is a little bit vague, and the imaging is very inconclusive in terms of interrater reading of the scans, do you think that in the community, people are convinced [inaudible] people have this in the same way? Or is there a lot of variability in determining who actually has this syndrome?

Mia Hagen: Right. So, the Tonnis is referring to the level of osteoarthritis that somebody has. I think the Tonnis scale is flawed, because of its reliability and a better proxy is really just weightbearing space, which you can measure and has high IRR. So, that's one problem with Tonnis. In terms of, like, the definition of femoroacetabular impingement and those bone angles, there is a widespread in literature in terms of exactly what degree we want to call that. The reason why that is, is because you're trying to quantify a three-dimensional structure with two-dimensional imaging. So, if you are looking at an AP pelvis radiograph and measuring a center edge angle off of that, that center edge angle is going to depend on the quality of that radiograph, as is the amount of cross-over. So, a cross-over sign is a measure of the amount of aversion of the acetabulum. That cross-over is dependent entirely on pelvic tilt. So, if you don't have a standardized radiograph, you can be over or undercalling that. Similarly, with the alpha angle, the area of impingement is the anterolateral portion of the femoral head. It depends on how that lateral radiograph is taken whether or no you'll capture that. The other thing that complicates not only those measurements is that . . . again, this is a dynamic process. Another thing that will go into whether or not there is impingement morphologically is the version of the femur itself. OK? So, the femoral neck can point forward or a little bit more backwards. Patients that have more retroversion of

their femoral neck are going to have impingement with a lower alpha angle and center edge angle, because their femur is pointed in a different direction. So, the struggle in the definition is because it's a three-dimensional structure. None of these 2-D measurements are going to quantify that. So, we make proxies based on these measurements, establishing alpha angle of 50 or 55, but there could be patients that have, if you got a 3D model and looked at their hip, they impinge at 45 degrees of an alpha angle, because of their retroversion. They're pointed backwards. So, that makes it hard. I 100% agree. The other challenging with the clinical examination is that there is no one test that is going to tell you that you have FAI. So, when I said that earlier, I was being a little more generalizing it, and that's the majority of the way that patients present, but all those tests, also will be positive if somebody's got hip arthritis. Right? They're all very nonspecific. Similarly, too, like, in the shoulder, the O'Brien test is going to be positive in anybody who has got a shoulder problem. It doesn't mean that you have a slap tear. So, that's why the Warwick Agreement I think was a step in the right direction to say that this is a really mixed . . . there's a whole lot of things that go into this diagnosis. You can't just say it's this and that. It's not as easy as saying that you, like, broke your femur. It's pretty complex. So, that was a very long explanation to your question.

Seth Schwartz:

Yeah, well what I'm struggling with a little bit, you know, is we look at a lot of spine topics, because there's a lot of these patients who say, OK. Well, radiographically, we see something's wrong with your spine, and you have pain. So, if we do surgery to remove this problem, you get better. So, there's a bunch of case series and cohort studies saying, you do the surgery and people get better, but then, you actually do a comparison to people who get physical therapy and basically it turns out the same. So, while as a surgeon you say, I operate on this person, they got better, I made them better. The reality is that it's not what's happening. So, this has this sort of same smell to it, which I'm sort of wondering about. While I completely understand you're [inaudible] surgeon. I know. I have the same thing. I fix you. You're better. I know that, but at the same time, we really have some degree of objective data, and we're looking at a couple of randomized trials, which I agree with you that some of the followup periods are fairly short, but the differences between the cohort is pretty minimal. So, I guess I would be curious if you have any comment about what a small difference that really is that we're seeing in these studies. I understand the point about followup, but as far as the degree of the difference that we're seeing is pretty . . . seems pretty minimal. So, I was curious if you have any comments about that.

Mia Hagen: Yeah. I mean, I think both of the larger trials that were shown met their MCID for their primary outcome, which varies depending on what you're looking at, but the confidence interval, again, is wide. So, I don't know how much of that is dependent on the shorter followup period or other biases that were introduced in the paper. So, I agree with you. There is definitely . . . it is hard to look at that data and say that this is helpful in remission, and it's going to make people better, but I would definitely challenge the committee to think of other, like, there are a lot of things in orthopedic surgeries . . . and I mention orthopedics, because that's what I know, that don't have any RCT's, that are, like, covered without question by insurers. So, it is . . . I think the amount of data that hip arthroscopy has accumulated in the last years has been really helpful to help further along this scientific question, but it's asking a lot to get a totally non-biased trial that can really answer the question definitively.

Gregory Brown: I will follow up on your comment. I think your analogy of the knee is perfect. We had no controls on hip arthroscopy and we're doing first debridements until we have RCT's showing that debridement doesn't help knee OA. Then, we do degenerative meniscus tears until we get metaanalyses of 25 studies showing that there is a small effect at six months. There has never been anything that shows that it delays time to a total knee. So, Health Care Authority and insurers are saying, we don't want to see that in hip arthroscopy until we have enough data to show that it doesn't work. So, I would say my distillation, I shouldn't say that. I've probably done three or four hip arthroscopies in my career, two of them, I take that back. I think I'm up to five. I think I did two in my fellowship. I think I did two at a level 1 trauma center where we had hip fracture/dislocations with a trapped piece of bone in the joint in a morbidly obese patient, and just the exposure to get there to take that out was going to be harder than trying to take it out with an arthroscope. Then, I think I did one in private practice five years ago, but anyway, my distillation of all this is, it will not delay any hip arthritis. In anybody over 30 or 40, it's a degenerative process, and we're in the degenerative meniscus tear grounds where it should not be done. So, I would . . . the indication essentially is pain. You can't measure pain objectively. So, you have this syndrome, which now has pain with radiographic findings and physical examination findings. So, if I had someone that is under 30, has an MRI documenting a labral tear and impingement anatomy, and they've tried three months of physical therapy and are not better, I would send them to you for surgery. You would hopefully agree with my diagnosis and that they've failed conservative treatment and offer them surgery. I agree with you completely, doing a labrum repair without fixing the bony malformation is just going to re-cause a tear six months, twelve months,

whatever down the road, is essentially malpractice, because you have not treated the cause. Anyway, agree, disagree?

Mia Hagen: I do agree with all that. I think the age thing . . . part of that is obviously the amount of arthritis. So, I've definitely had people in their 20s who have close to bone on bone arthritis who would not be candidates for hip arthroscopy, and I've also had 40-year-olds with perfect looking cartilage with no acetabular edema or cystic changes on MRI. When you look at their joint, the cartilage looks like a 20-year-old. So, I think age is a little bit . . . it can't be the only factor. It definitely has to do with the amount of degeneration in the joint.

Janna Friedly: The challenge from an evidence standpoint is that none of that is borne out in the evidence. There's no way for us to be able to . . .

Gregory Brown: No. No. And that's why I say.

Janna Friedly: Yeah.

Gregory Brown: Essentially, I am using the analogy of knee meniscus tears. Again, it's the same pathway. We started doing debridement. It didn't work. Then we went to debriding degenerative meniscus tears. It didn't work. Whereas, if you are 20 and get an ACL tear and a meniscus tear, you try and repair that, because you know a resected meniscus in a 20-year-old will lead to arthritis. So, you're right. Where you lack the evidence in the hip joint, you do have strong evidence in a very similar condition in another joint with robust evidence, and that evidence supports the failure of overutilization of a procedure. So, you're avoiding that. I would agree with you. Instead of age, do MRI grading, anything more than grade 1 changes in the cartilage on an MRI is a contraindication to arthroscopy.

Janna Friedly: It sounds like you need to do that study.

Mia Hagen: Well, there are prospective studies looking at the amount of . . . correlating radiographic changes and outcome with preservation surgery. So, all of those show that if you operate on someone with greater than Tonnis 2, which albeit it is a bad classification, or less than 2 mm of joint space, that they're not going to do as well.

John Bramhall: We're being asked to look at a procedure in sort of isolation as a procedure, but I got the sense in your opening comments that there is a high degree of skill that is required to execute this procedure correctly, safely, effectively. How would that play into our decision process, do you think? Could it? I mean, the implication is that you have a procedure done

by ten different surgeons, two of whom are highly skilled, two of whom are rudimentary skills, there's going to be an outcome difference.

Gregory Brown: Is endoscopic carpal tunnel, spine surgery, certain procedures, lasers, robotic surgery requires documentation of a volume to be able to do the procedure. So, you set a threshold, a surgeon has to do X-number a year to be . . . we're back to this best Center of Excellence concept that we just had in the morning, to be a qualified surgeon to do this. The problem is, you get someone who did a sports fellowship, and they do lots of them, and they do them really poorly. So, they meet all the criteria, and they operate on anybody that walks in the door.

Mika Sinanan: I had a question. You said the patient somehow get them anyway. They make a change in their coverage. So, do you have a feeling, a sense, that the lack of coverage right now is harming patients?

Mia Hagen: 100% yes. I have seen it almost every day in clinic. We limit . . . I actually don't see patients now with certain insurances, because unless they know up front that I cannot offer them a surgery, and they're OK with that, which is not usually the case, because it's been a really . . . a lot of . . . we've had a lot of trouble in our clinic when patients come in, I haven't paid attention to what their insurance is. I tell them this, that, and the other thing about their hip. Then they can't the surgery, so they are writing angry letters to the University of Washington, etc. So, a lot of those patients have found other pathways. So, for L&I for example, they go off of L&I and use commercial insurance if they have access to it. Patients that are on a commercial payer that doesn't cover, like Regence Uniform, switch during open enrollment. Other patients that can afford it, we have a package price now that we offer. So, if they can afford it, then they pay that.

Mika Sinanan: Thank you, and do you use a protocol of a period of physical therapy first and then some defined level of lack of improvement before . . .

Mia Hagen: Yes.

Mika Sinanan: . . . you offer them surgery?

Mia Hagen: They have to completed minimum six weeks, but usually more like three months of physical therapy.

Mika Sinanan: If a coverage decision was developed, would you recommend that that be an inclusion criteria?

Mia Hagen: 100%.

- Mika Sinanan: What kind of a time limit?
- Mia Hagen: I think a minimum six weeks of formal physical therapy.
- Mika Sinanan: And do you have to specify it beyond that? I mean, does . . . just saying physical therapy is enough? Or . . .
- Mia Hagen: I do think it has to be . . . OK. I take that back. I strongly believe that formal physical therapy is better than a home exercise program for hip specific conditions, because of a lot the patient cuing that's needed for it to correct postural imbalances. A lot of the soft tissue work and traction that's done. So, I think . . . but to say that it has to be formal . . . I think if I were to make a policy, I would request six weeks of formal physical therapy, since that's what the RCT's have looked at. The treatment group, the nonoperative groups have all had formal PT with activity modification. Did that answer your question?
- Mika Sinanan: It does. There are a lot of orthopedic surgeons who don't take Medicaid around the state. So, a coverage decision would tend to send the patients in a certain direction.
- Kevin Walsh: I'm going to ask before we pursue coverage decisions, that we share our thoughts about what we think the evidence says about this procedure.
- Sheila Rege: So, I would echo both those thoughts. Janna's thought, too, that the evidence just . . . we're charged with making recommendations on the safety, cost-effectiveness, etc. Based on the evidence. I think anecdotally, I feel for patients, but unless a committee is given that as a task or allowing that, I think we need to focus on the evidence for our discussions.
- Mika Sinanan: I agree, but I also . . . what I was exploring was the consequences both directions. And that's what the consequences are.
- Gary Franklin: Could I just ask if you formally collection functional status data at baseline, like six months and a year and you have that, and you could have presented that if you had it, do you have that kind of data and what have you seen with that data?
- Mia Hagen: So, I have an informal QI project for hip arthroscopy. I collect preoperative and six-month and one-year patient priority outcome measures. The challenge is loss to followup. I don't have a research team. So, I can't ensure that I have high followup rates. My one year followup is about, like, 5% of that cohort. People just don't come back. Assumedly, they're doing

well. They come to their six month. They look good. And they don't come back for their one year. So, I have good six month data, but the one year I don't have as much of. I would say, so what my own cohort that I collect is definitely a less robust database than what is accessible, for example, at the OME at the Cleveland Clinic. So, they have 85, 90% followup at one year, because they have a \$250,000 budget to do so, but I do collect that, only in hip, though, not in other parts.

Laurie Mischley: I was curious, given that there is a little bit of a disconnect with the evidence, but then what you see clinically, has using dynamic musculoskeletal ultrasound help close the . . . is it truly bone impingement question at all where you can actually see it mechanically impinging with the ultrasound?

Mia Hagen: I'm not aware of any studies looking at ultrasound to assess that. There are 3D CT and MRI modeling studies that have shown that, and all of that show that if you have volumetric data, you are much more precise about characterizing impingement, but I don't know of any ultrasound studies. The main use of ultrasound around the hip seems to be mostly for the purpose of injections.

Gregory Brown: OK. Evidence, should we go to our tool, or any more discussion first? Safety, [inaudible] classification, I didn't hear anything. AVM, I didn't hear anything. Femur fracture, again, didn't hear anything. I did hear somewhere nerve injuries, transient.

Sheila Rege: Didn't I hear something on HDO, or maybe that was just my reading?

Mia Hagen: So, heterotopic ossification has been reported historically in hip preservation surgery, due to dissection through the adductors. In arthroscopy, when you do see that formation, it's a [inaudible] of one at most. It's, like, a dot of bone. It's never anything like [inaudible] four or anything spanning the joint.

Gregory Brown: Certainly, revision surgery, either conversion to total hip or revision arthroscopy is there. I think one study showed two infections if I remember our review. I didn't hear anything about embolism or venous thromboembolic issues. Revision surgery is here twice and thrombosis same thing. I didn't hear anything there. Actually, I didn't hear on evidence on repairing your capsulotomy. Is that something you do? Is that a best practice now?

Mia Hagen: I think it is becoming best practice. I do that routinely in all of my cases, due to the low quality comparative cohort showing that capsular repair

- does better than debridement or leaving your capsulotomy open. So, that is something that I do, but it definitely is an extra added technical challenge.
- Gregory Brown: Anyway, any other safety issues that . . .
- Seth Schwartz: Talking about femoral head fractures and that sort of thing.
- Gregory Brown: Yeah, I mean, I think the concern actually is an over aggressive femoral neck osteoplasty. So, you basically undercut the head and get a stress riser. Again, I think that's exceedingly rare, especially in a high volume surgery.
- Mia Hagen: More historic, yes, but if you resect more than 30% of the femoral head and neck area, you could put someone at risk. That is a lot of bone to take out. Usually it is only done if you're doing this open.
- Gregory Brown: OK. Any other comments on safety, or are we ready to do our real vote? So, safety, hip arthroscopy versus physical therapy. More safe, less safe?
- Josh Morse: I'll count less first, one, two, three, four, five, six, seven, eight, nine, less, one equivalent.
- Gregory Brown: Efficacy, I think the short-term followup, well, let's review these, function, there are studies at some shorter followup showing potentially better pain with surgery. Question of how much and for how long. I don't think, again, there's no longterm function. I think conversion to hip is . . . if that's your outcome measure, you're looking at the wrong thing. That's hip arthritis, not . . . again, I think the indication in the younger person is pain and/or return to sports, which is probably quality of life for them. I don't think anybody is reporting range of motion, return to work I didn't hear any evidence on return to work, which would be an L&I outcome. Again, progression arthritis, I don't think there's any evidence that delays progression of arthritis. So, yeah.
- Erika Brodt: I just wanted to say the only evidence on return to work was from Mansell, and it was return to active duty. There was no difference between the groups.
- Gregory Brown: I will tell you, in the orthopedic community, that the military surgeons basically consider themselves sports medicine surgeons. They do very few joint replacements, and they virtually do all sports medicine kinds of things for acute injuries and athletes, but they're soldiers, which is their work. Any other outcomes that we're missing here that we need? OK. So,

- efficacy, arthroscopy versus PT, better in some or more in some in patients, arthroscopy as far as pain as our main outcome. More pain relief with hip arthroscopy in some patients.
- Josh Morse: I'm going to count more and some first. There is one, two, three, four, five more in some. Unproven one, two, three, four, five unproven.
- Gregory Brown: Cost and cost-effectiveness. I find the NHS study compelling. I think it is applicable. The difference is, is the United Kingdom is willing to put a threshold on what they'll spend where we're unable to do so in this country. I don't think the . . . studies done in the U.S. are fundamentally flawed, estimating progression, changes in progression of arthritis and things like that. They're just pulling numbers out of the air. Comments or issues? So, we're voting on cost-effectiveness, not cost. So, cost-effective is less cost-effective is hip arthroscopy is less, less cost-effective than therapy. Does that make sense? I think I'm . . . conditioning your vote response by how I say it.
- Josh Morse: I'll count the unprovens first. I see one, two, three, four, five, six, is that right? One, two, three, four five, six unproven, and one, two, three, four less cost-effective.
- Gregory Brown: Are we ready to vote on cover, cover with conditions, or not cover?
- Josh Morse: I'll get started counting, and Dr. Mischley will make up her mind. We'll start with not cover. I count one, two, three, four, five, six, seven, eight, not cover. One, two cover with conditions.
- Gregory Brown: I think we have our answer.
- Josh Morse: So, there are two additional questions in your guide.
- Gregory Brown: So . . .
- Josh Morse: Is the decision consistent with a National Coverage Determination if there is one?
- Gregory Brown: So, Medicare doesn't have any coverage decision is my understanding.
- Josh Morse: I think it was reported there was no National Coverage Determination.
- Gregory Brown: There is no formal clinical practice guidelines. There's the Warwick Agreement and the Lynch 'best practices,' but no . . . there's no, like I said, no National Medicare Coverage.

Josh Morse: OK. Thank you.

Mika Sinanan: Can I, with regard to our next year's retreat, I think we had two interesting situations today. One is an evolving technology and an evolving cost structure, which we're trying to anticipate based on the available evidence where it's going to go and provide a reasonable recommendation for that application in the future. So, that's a specific strategic discussion topic is how we think about that. Rapidly evolving technology and cost where the efficacy of the technology is changing, and we can actually draw the curve, and where the cost is also changing. How do we think about those separately from something that's rapidly changing relative to our current . . . relative to the rules if it requires anything different, but I think part of our discussion focused on that. Then, the second topic is this one where Laurie, you've made the point before about the importance of observation cohort studies and about how we tend to prioritize Health Technology Clinical Committee over nearly everything else, because it's the most easily understandable comparator, but it may not capture the kind of evidence that you've provided, especially will make any surgical study a harder study to do, because you can't as easily do an RCT, and you can't blind them. So, I think that that's a second topic of do we think about those in the same way? Is there a more structured way to think about it where we say this is . . . it's one of those kinds of studies, let's add one or two other questions. For example, perhaps invite our clinical expert to prepare in a different way, to bring us additional data, or at least to provide a different perspective than they currently do.

Kevin Walsh: I disagree with asking the clinical expert to provide different data, because I think we have established very clear criteria about what are acceptable data, and I am not . . . that would have to be more people than us making that decision. I'm not comfortable with that idea.

John Bramhall: I mean, we get that data anyway.

Mika Sinanan: We just get it in a off the top of their head, as opposed to thinking about it. That's my point.

John Bramhall: But the difficulty we have, just an embarrassing difficulty is that we, as Sheila says, we're forced to follow the data. That's what we do. Yet, we have a highly experienced person in a particular technology who gives us completely different view on it, which we then ignore, because it's not relevant to the structure of the committee, and that's a little dissonance there that is awkward, I think.

- Kevin Walsh: I agree with you, but I feel like the awkwardness has to do with the paucity of good studies done by the specialty that's being represented by the clinical expert.
- John Bramhall: If we had the good data, we would be making different decisions. Right.
- Kevin Walsh: If they gave us better data, maybe it wouldn't even be something we had to discuss, because the agency would feel comfortable with what the studies indicated.
- Mika Sinanan: One way to think about it, for example, is a more routine question of, you've seen the analysis, you've heard the presentation, you hear the tenure of the questions, does your clinical experience match that? And if not, why not, based on your expertise? Because I think that's an important clinical point at least in a . . . it may not be something that we can use because we are required to use the data, but I think it's important to acknowledge the fact that there was a difference, a delta, in the discussion.
- Sheila Rege: I think the clinical expert brings that, but I think what I see the clinical expert as, kind of what she said, you know? Look at whichever that study was where . . . the army study where there was a 60 or 70% cross-over. The clinical expert is able to parse out the data we're seeing and give us an opinion on that. I see the clinical expert's role as that. What she or he does in their personal clinic, they do it because they believe in it. I could believe that, for example, in oncology, this big thing is you put these cold gels on your head and you don't lose your hair with chemotherapy. Well, I'm going to keep doing it, if I believe it. That's anecdotal until there's data. So, I'm not convinced . . . I mean, I understand that the person may have experience in that, but what I expect that person to say is, you missed a study, or there's a problem with that study, because there was cross-over. That's where I rely on the clinical expert more, but that's personal, because I feel my charge is to look at the data and make a decision based on the data.
- Mika Sinanan: I think it's both. I would just ask you, if you were asked only to come here and comment on the validity from your perspective of the studies that we had been receiving from the reviewer, as opposed to expressing anything of your own practice or opinion and observations, I think it would be a less valuable experience for you. I think we would be losing, I'm especially struck by the fact that you said 100% of the time, we are potentially harming people. That's an important data statistic. I still voted not to cover it, but I think it was important to know and capture.

- Seth Schwartz: I think it's an important piece of historical context, too, because historically, we did not ask the clinical expert to look at the data at all. We asked them for their clinical perspective on the condition. So, I think to devalue that at this stage doesn't make any sense. I think by having the expert at the table, we're allowed to invite them to participate in the data discussion, but their role as a clinician is really what's key here. So, I don't know that I would say bring us, you know, bring us your personal experience data, but I think reflecting on what your personal experience is, I think, is value.
- Mia Hagen: I think something that you said, Dr. Sinanan, really struck me, though, is that surgery . . . it's so hard to do well structured RCT's. There needs to be another way to evaluate this data and look at it. It's similar to the moon cohort in ACL. That's just a prospective, a very well run registry, essentially.
- Gregory Brown: There is a mechanism, and both vendors talked about it, a well done observational prospective outcome cohort can be upgraded to moderate evidence. It starts at low, but I can be upgraded. The other thing, I agree with you Kevin. I actually, I guess as my parting statement, the fact that this is a review, or a rereview, speaks to the process. So, what we as a committee said is, we made a decision several years ago. There's new evidence out there. This review says there's more evidence. It's better than we had, but it still isn't good enough. We still need better evidence before we're going to say this is an approved treatment. That's a good process. We're not saying don't ever come back. We're saying you're better, but it's still not good enough. So, I agree with Sheila. I mean, I agree with all . . . this is an evidence based process. It has to be an evidence based process. Even if you do have your own data, if you don't have it published, it's not evidence. So, it's anecdote. We went through that with trying to use some of the scope spine outcome data that wasn't published and trying . . . anyway . . .
- Mia Hagen: Right. So, I think that's where the trouble was is that those studies exist, they're just not presented in this format.
- Seth Schwartz: And I think this is sort of a unique situation where when we look at surgical interventions, we almost never have randomized trials. So, we're universally looking at these cohort studies and looking data like scope and things like that where we want to track outcomes. Those are clearly biased towards a positive outcome for all the reasons that we know about. So, I think this condition, in some way, is challenged by the fact that there are randomized trials. So, they didn't dig deeper in the evidence to look at the . . . to bring us those cohort studies. I guess we saw a few of them but

nothing really extensive, but we looked at them much less seriously than we normally would, because we had the randomized trials. You often don't see this. If you do a case series or cohort studies, it looks like there is an effect, and then you put it up to the test of a randomized trial, and it doesn't really hold up. So, I think that's the situation here is that we have randomized trials, and they haven't been really able to show efficacy when you hold it to that bright of a light. So, I think more data but where we are now is just . . .

Kevin Walsh: This is one of the best orthopedic study . . . I mean, this is one of the best group of studies I think I've seen in orthopedic literature for us to review, because they compared it to something. Oftentimes in orthopedics, they don't compare it to anything.

Seth Schwartz: I would generalize that broader than orthopedics.

Mia Hagen: That's one of the [inaudible] for me. I mean, coming into here, I knew it wasn't going to be approved based on the data, but then it's, like, if you look at anything that we currently do in ortho, I don't think anything has even close the amount of data that this does. It feels unfair.

Seth Schwartz: But there's also the question, why is this under this level of scrutiny. So, there's a lot of interventions, it's clear, right? You got a fracture, you fix your fracture. You're not going to study that. There's a lot . . .

Mia Hagen: I think the reason it's under that scrutiny is because it's been done incorrectly for so long when people were doing this as, like, a debridement for arthritis.

Seth Schwartz: That may be part of it. I think the other issue is when you have pain outcomes, you're struggling. So, when you have clear functional or morphologic features that you're trying to fix with surgery, you have a definitive outcome. You don't necessarily need to study it. Whereas pain is such a subjective outcome. We know that with almost all pain conditions, there is a massive amount of regression to the [inaudible]. So, it's really hard to . . . so, if you're going to do an intervention that has some risk to it for pain, you have to be able . . . I think those standards should be higher to prove that it works.

Gregory Brown: I have to make a presentation. So, since the arrogant orthopedic surgeon is leaving the committee, we needed somebody to fill my shoes. So, we have [inaudible].

Group: [Laughs]

Mika Sinanan: Do I have to wear this at every meeting? So, at least I can take my [inaudible].

Gregory Brown: Only on surgical topics.

Mika Sinanan: Just for surgical topics. So, that's not the solution I was thinking of. Thank you.

Gregory Brown: I guess technically, you have 15 minutes of updates. Do you have any updates.

Josh Morse: I will give two brief updates. We will be opening recruiting for this committee, because Dr. Brown is departing. So, we have not published that yet, but we will be releasing that. So, if you have people that you think might be interested or that you want to recommend, we will send out that email to you. Or if you just on your own want to send in names, we welcome that. I think that's my only update. So, thank you, very much, for your hard work today.